



# THE JOURNAL OF GENERAL PHYSIOLOGY

*Founded by Jacques Loeb*

EDITORS

W J CROZIER

JOHN H NORTHROP

W J V OSTERHOUT

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## THE JOURNAL OF GENERAL PHYSIOLOGY

EDITED BY

W. J. CROZIER

JOHN H. NORTHROP

W. J. V. OSBORN

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VOLUME TWENTY EIGHTH

WITH 2 PLATES AND 229 FIGURES IN THE TEXT





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# NATURE OF THE GROWTH FACTOR FOR THE COLORLESS ALGA PROTOTHECA ZOPFFII

By EDWARD H. ANDERSON

(From the Hopkins Marine Station of Stanford University, Pacific Grove)

(Received for publication September 26, 1944)

The detailed studies of Barker (1) on the metabolism of *Prototheca zopfii* demonstrated that development of this organism did not take place in media containing a suitable carbon source and inorganic or amino nitrogen only. Yeast autolysate or some other source of complex organic material was found requisite for development. The quantity of yeast extract required for growth, however, was very small. In media containing low concentrations of this material development of the organism could be greatly increased by the addition of an ammonium salt such as ammonium chloride. Although this substance could not serve as a substitute for yeast autolysate, quantitative studies showed that a large portion of the nitrogenous cell material could be synthesized from the ammonia nitrogen. The maximum cell yield of *Prototheca* was shown to be a complicated function of the amounts of yeast autolysate and ammonia nitrogen available. From these experiments Barker concluded "Yeast autolysate or some other complex material is indispensable for the development of this alga."

It seemed logical to investigate the possibility, indicated in the findings of Barker, that yeast autolysate contributed one or more essential growth factors. A detailed study of this phase was attractive because the identification of such factors would make it possible to investigate their function in the metabolism of this organism.

## Material and Methods

**Organism**—The strain of *Prototheca zopfii* used was No. 7322, one of the several maintained in the pure culture collection at the Hopkins Marine Station. It was selected from the group on the basis of its rapid development in a simple liquid medium.

**Medium**—Cultures of the organism were maintained on yeast agar containing 2 per cent glucose.

For studies on the growth factor requirements of the organism, a basal liquid medium of the following composition proved satisfactory

	per cent
Glass-distilled H <sub>2</sub> O	
NH <sub>4</sub> Cl	0.10
MgSO <sub>4</sub>	0.02
KH <sub>2</sub> -Na <sub>2</sub> HPO <sub>4</sub> (pH 7.0)	0.20
Glycerol	0.50



For growth factor studies it is imperative that all tests for substances, functioning as nutritives for a particular organism, be carried out in a basal medium which is as simple as possible and yet contains *all* other elements necessary for growth of the organism. The composition of the glycerol mineral medium fulfills these requirements closely enough, since in the absence of yeast extract or of the active components of this material practically no growth occurs, whereas the addition of these materials gives rise to a profuse development.

Glycerol was chosen as a carbon source in preference to glucose because glycerol is not acted upon by *Prototheca* under anaerobic conditions. While glucose is aerobically converted into cell material and carbon dioxide, anaerobically it is quantitatively fermented into lactic acid (1). Therefore, the use of glycerol has the great advantage over glucose in that the acidity of the medium resulting from the growth of the organism on glycerol will be solely that arising from fermentation of stored carbohydrate products. This obviates the necessity of the addition of large quantities of calcium carbonate to the culture medium as a buffer. Glycerol has the added advantage as a substrate for growth factor tests in that it does not undergo decomposition or polymerization when sterilized in the presence of phosphates as does glucose. The products resulting from heat sterilization of sugar have been found to influence the growth of microorganisms, exerting a toxic effect on some and acting as growth-promoting substances for others (Stanier (2), and Fulmer, Williams, and Werkman (3)). Finally, glycerol can much more easily be obtained free from minute amounts of organic impurities, which might serve as growth factors, than can carbohydrates.

To determine if autoclaving resulted in a serious destruction of growth factors, duplicate series of varying concentrations of yeast autolysate were prepared using sterile autolysate and heat-sterilized medium base. One series was autoclaved at 15 pounds pressure for 20 minutes and both series were inoculated with equal amounts of a dilute *Prototheca* suspension. Cell yield determinations for each series indicated conclusively that under the conditions employed in the tests the growth promoting substances are quite heat-stable and that sterilization may be safely accomplished by autoclaving.

Glassware used for all growth factor experiments was scrupulously cleaned with cleaning solution and at least four final rinsings with distilled water.

*Culture Methods* —Although *Prototheca* is capable of carrying on an anaerobic metabolism it is totally unable to develop under strictly anaerobic conditions (1). In tests for the activity of growth factors it is essential that the conditions of aeration approach the optimum in order that the growth of the organism will be a function of the amounts of the growth substances present rather than being restricted by a limited oxygen supply. Quantitative experiments were therefore carried out with cultures in shallow layers in rotating bottles. Unless otherwise stated these cultures were incubated at 30° C for a period of 7 days.

Although satisfactory growth curves were obtained with cultures growing in liquid media dispensed in 50 ml volumes in Florence flasks of 125 ml capacity, such curves

indicated reduced oxygen tension to be a limiting factor in the growth of *Prototheca* in flasks. This was especially true at the higher concentrations of growth-promoting substances. To obtain more nearly optimum aerobic conditions under which to grow *Prototheca* a method of culture was devised which would allow the surface of the liquid medium to be very large as compared with its volume. This was accomplished by using 25 ml. volumes of medium in 150 ml. narrow mouth glass bottles having an inside diameter of approximately 5 cm. When the bottles were placed on their sides the greatest depth of the liquid was about 1 cm. To further insure uniform aerobic conditions the bottles were placed in a rolling machine and continuously rolled at the rate of about 18 R.P.M.

In order to compare the growth of *Prototheca* in 25 ml. amounts of medium in bottles with that in 50 ml. amounts in flasks graduated series of concentrations of yeast autolysates were set up in each type of culture vessel and incubated for a period of 10 days. Cell yield measurements for each series are recorded in Fig 1. These

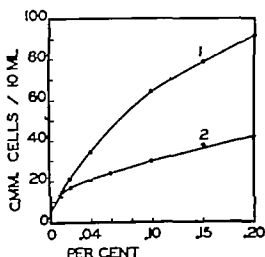


FIG 1 Comparison of the growth of *Prototheca* in bottles (1), and in flasks (2), in media containing varying concentrations of yeast autolysate.

clearly demonstrate that growth of *Prototheca* in flasks under semi-aerobic conditions is definitely inferior to that produced under aeration such as is obtained in shallow layers continuously rolled. Further experiments showed that with the higher yeast extract concentrations double the amount of growth could be obtained in bottles in 1 week as that obtainable in flasks during a 2 week period of incubation.

**Quantitative Determination of Cell Yield**—Determination of cell yield was accomplished by centrifuging aliquot portions of the cultures. Ordinarily, 10 ml. were centrifuged in Hopkins vaccine tubes for 10 minutes at 2700 R.P.M. The results so obtained are quite reproducible and of an accuracy sufficient to show a linear relationship between cell volume and the amount of growth factor in the lower concentrations of this material.

#### *Fractionation of Yeast Autolysate and Activity of the Fractions*

Since Barker had shown yeast autolysate to contain substances essential for the growth of *Prototheca* this material was selected as a source from which to

attempt the isolation of the active constituents. Preliminary extraction tests using ether, chloroform, and 95 per cent ethanol as solvents were carried out on aliquot samples of yeast autolysate adjusted to pH 2.5, 7.0, and 9.0. The autolysate used in these tests was prepared by letting pressed yeast autolyze in the presence of chloroform according to the method of Willstatter (4). Additional extractions using ether and 95 per cent ethanol as solvents were carried out in a Soxhlet extraction apparatus on a dehydrated yeast extract powder (Difco standardized). Appropriate amounts of the soluble and insoluble fractions obtained for each pH value for each solvent were mixed with the basal medium to provide a wide series of media for each fraction. These were inoculated with equal amounts of a *Prototheca* suspension. Cell volume determinations made on aliquot samples from each culture showed that the growth-promoting substances for *Prototheca* are not extracted by ether or chloroform from acid, neutral, or alkaline solutions, as in each case the total activity remained in the insoluble fraction. Cell yield values obtained in the series of media containing the various ethanol fractions showed that the nutritives for the alga are alcohol-soluble. In addition, growth of the organism in the fractions obtained in the alcoholic extraction of yeast autolysate which had been adjusted to pH 9.0 indicated that the growth-promoting substance had undergone some destruction.

*Comparison of Active Material with Known Growth Factors*—The solubility characteristics of the active substance in the various solvents tested, strongly suggested the possibility of its association with the group of B vitamins known at the time these investigations were undertaken. More specifically, its sensitivity to alkali indicated a striking similarity to the properties possessed by vitamin B<sub>1</sub> (thiamin). Consequently, a number of experiments were set up with the mineral glycerol medium, to which a graded series of concentrations of three members of the B group (thiamin, riboflavin, and nicotinic acid) had been added. Growth determinations showed that only those media which contained vitamin B<sub>1</sub> permitted development of *Prototheca* and that the further addition of riboflavin and nicotinic acid did not result in any greater cell yield than was obtained with thiamin alone. The maximum growth in the presence of thiamin alone approximated closely that previously observed in the presence of yeast extract. Comparative experiments using the basal medium enriched with yeast autolysate and with thiamin in different concentrations corroborated this. Additional experiments, in which combinations of low concentrations of yeast autolysate and thiamin were used, showed the activity of the two materials to be additive. Serial subcultures in the glycerol medium with added vitamin B<sub>1</sub> have shown *Prototheca* capable of the same level of growth for many transfers.

These tests consequently established the chemical nature of the factor which is responsible for the activity of yeast autolysate in the growth of *Prototheca*. It can be asserted that the only nutritive required by this alga is thiamin. Its

activity is very high, concentrations as low as  $3 \times 10^{-11}$  M permit a detectable growth of the alga. The response to increasing concentrations of thiamin is shown in Table I and part of the data has been plotted in Fig. 2. This figure shows that the relationship between thiamin concentration and cell yield is virtually linear to  $1 \times 10^{-7}$  M thiamin. At this concentration growth is practically as heavy as the maximum obtainable with larger amounts of the vitamin. Considerably higher concentrations of vitamin B<sub>1</sub> seem to show a tendency

TABLE I  
*Growth of Prototheca in Various Concentrations of Thiamin*

Molar concentration of thiamin	Cell yield	Molar concentration of thiamin	Cell yield
	mm. <sup>3</sup> per 10 ml		mm. <sup>3</sup> per 10 ml
$1 \times 10^{-10}$	7	$5 \times 10^{-8}$	56
$3 \times 10^{-10}$	9	$8 \times 10^{-8}$	80
$1 \times 10^{-9}$	12	$1 \times 10^{-7}$	96
$3 \times 10^{-9}$	15	$3 \times 10^{-7}$	110
$1 \times 10^{-8}$	20	$1 \times 10^{-6}$	105
$2 \times 10^{-8}$	32	$1 \times 10^{-5}$	100
$3 \times 10^{-8}$	40	$3 \times 10^{-5}$	97

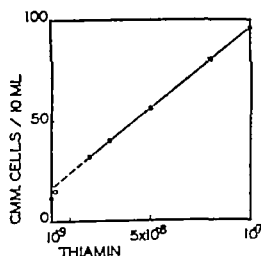


FIG. 2 Relationship between molar concentration of thiamin and cell yield

exert a slight inhibition. Although the accuracy of determination of cell yield at this cell concentration is insufficient to stress this depressant effect, it may be stated that such results were consistently obtained and that Schopfer (5) has made similar observations.

#### *Thiamin and Its Components As Growth Factors*

**Thiamin Requirements of Plants and Animals**—The general need for thiamin—as a vitamin for animals, as a necessary growth factor for many microorganisms, and as a hormone (6) for plant cells—shows that it plays an important rôle in the growth of the most diverse types of cells.

The elucidation of the chemical configuration of thiamin and its simple quantitative cleavage into the thiazole and the pyrimidine portions has made possible detailed studies concerning the replaceability of thiamin by its major constituents and by laboratory-synthesized analogues of these constituents. This approach has revealed that both the higher and lower animals require the complete thiamin molecule. Even the protozoa not obviously derivable from algae (ciliates, trypanosomes) behave in this manner. On the other hand many plant tissues and plant-like microorganisms are less exacting and are capable of fulfilling their thiamin requirements from a mixture of the two components of the thiamin molecule as effectively as from the whole molecule. Some of the microorganisms are even able to satisfy their growth requirements from the thiazole or the pyrimidine component supplied singly. In this connection it is interesting to note that certain of the fungi considered as typical plant parasites, resemble the animals in that they require the entire thiamin molecule for growth.

The microorganisms can thus be divided into five groups according to their relationship to thiamin and to its components.

(a) Organisms requiring the whole thiamin molecule. The Lwoffs (7 to 10) have shown the ciliate *Glaucoma piriformis* and three species of the flagellate *Strigomonas* to resemble the animals in their vitamin B<sub>1</sub> requirements, Robbins (11) reports ten fungi of the genus *Phytophthora* to likewise require the complete thiamin molecule.

(b) Organisms needing thiamin or both of its components in equimolar concentrations. Knight (12) showed *Staphylococcus aureus* to need thiamin or its components for growth, neither part alone functioning in this capacity. Similar findings were made for the molds *Phycomyces blakesleeana* and *Phycomyces nitens* by Schopfer and Jung (13) and by Robbins and Kavanagh (14) and by Sinclair (15). Schopfer (5) found the fungus *Pilaira moreaui* to require both components also. Lwoff and Dusi (16 to 18) broadened the known list of organisms capable of utilizing mixtures of both components with their findings for the flagellates *Polytoma caeca* and *Chlomonas paramecium*. Robbins and Kavanagh (19) included the yeast *Torula laurentii*, and the basidiomycetes *Ustilago violacea* and *U. scabiosae* were added by Schopfer and Blumer (20).

(c) Types of organisms requiring only the pyrimidine component. In the long list of fungi whose growth factor requirements were investigated by Schopfer (21) we find five species of *Rhodotorula* and one of *Dematium* representing the yeasts, and the zygomycetes *Absidia ramosa*, *Parasitella simplex*, and *Pilaira anomala* which are capable of satisfying their growth factor requirements from the pyrimidine component alone. Robbins and Kavanagh (22) found two representatives of *Pythium* and one of *Phytophthora* to include in this type.

(d) The fourth group of organisms, those capable of utilizing the thiazole portion alone, includes *Mucor ramannianus* (Müller and Schopfer (23)), and the protozoa *Polytoma caudatum* (Lwoff and Dusi (17)), and *Polytoma ocellatum* (Lwoff and Dusi (24)). It may be pointed out that these two species of protozoa are related to the *Chlamydomonas* group of green algae and thus can be expected to possess thiamin requirements characteristic of the plant-like organisms.

(c) The fifth type comprises a large group of bacteria, yeasts, molds, and algae which are capable of normal development in the absence of any external source of thiamin or its components.

*Identification of the Growth Factors for Prototheca zopfii*

Although thiamin was found to satisfy the growth factor requirements of *Prototheca*, further tests were made to determine whether this organism needs the whole vitamin molecule, a mixture of the thiazole and pyrimidine components, or one of the components alone as the active principle

TABLE II  
Cell Yield in  $\text{Mm}^3$  per 10 Ml of *Prototheca* Cultures Grown in the Presence of Different Concentrations of Thiamin and of Various Pyrimidine Preparations

Molar concentration	Thiamin	Pyrimidine						
		3	3 B	4	5	5 W	6	7 M
$5 \times 10^{-6}$	104	8	9	8	7	7	4	10
$1 \times 10^{-6}$	94	8	9	8	7	8	4	7
$5 \times 10^{-7}$	96	8	9	8	7	8	4	8
$1 \times 10^{-7}$	94	8	7	8	7	7	4	8
$5 \times 10^{-8}$	86	8	7	8	7	9	4	7
$1 \times 10^{-8}$	32	8		8	7	9	4	7
$5 \times 10^{-9}$	17	8	7	9	7	8	4	7
$1 \times 10^{-9}$	6	6	7	8	7	8	4	5
Control	2							

3 = 2-methyl-4-amino-5-aminomethyl pyrimidine

3 B = 2-methyl-4-amino-5-aminomethyl pyrimidine

4 = 2-methyl-4-amino-5-hydroxymethyl pyrimidine

5 = 2-methyl-4-amino-5-chloromethyl pyrimidine

5 W = 2-methyl-4-amino-5-chloromethyl pyrimidine

6 = 2-methyl-4-amino-5-aminomethyl pyrimidine

7 M = 2-methyl-4-amino-5-ethoxy pyrimidine

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*Growth of Prototheca on the Thiazole and on the Pyrimidine Component*—In experiments conducted to determine the ability of the alga to grow on thiazole or pyrimidine alone, media containing various concentrations of five thiazole preparations<sup>1</sup> and seven pyrimidine analogues<sup>1</sup> were made up in glycerol mineral medium and sterilization was accomplished by autoclaving.

Cell yield measurements in media containing pyrimidine alone showed about equal but very slight development for all samples, with one exception, and in no case did an increase in concentration over a 5,000-fold range cause an appreciable increase in cell yield. Data for these growth tests are presented in Table II.

<sup>1</sup> These preparations were kindly supplied by the I. G. Farbenindustrie, Winthrop Chemical Company, Merck and Company and Dr. James Bonner and Dr. E. R. Buchman of the California Institute of Technology.

The results obtained with four different samples of 4-methyl-5-hydroxyethyl thiazole and one sample of the benzoic acid ester of the same compound are recorded in Table III. They show that, while the benzoic acid ester was without any activity whatever, the effects of the four "natural" thiazole compounds on the growth of *Prototheca* were far from comparable. Cell yields ranged from an amount equal to that obtained in the controls to very nearly the maximum volume obtainable from growth on the whole vitamin. Since the thiazoles used in these tests were different preparations of the same compound, the purity of those permitting heavy growth was not above suspicion. Additional growth

TABLE III

*Cell Yield in Mm<sup>3</sup> per 10 Ml of Prototheca Cultures Grown in the Presence of Different Concentrations of Thiamin and of Various Thiazole Preparations*

Molar concentration	Thiamin	Thiazole				
		1	1 W	1 M	1 B	2
$5 \times 10^{-6}$	104	70	86	84	21	2
$1 \times 10^{-6}$	94	24	42	90	10	2
$5 \times 10^{-7}$	96	18	28	84	6	2
$1 \times 10^{-7}$	94	9	12	51	2	2
$5 \times 10^{-8}$	86	7	8	33	3	2
$1 \times 10^{-8}$	32	4	3	12	3	2
$5 \times 10^{-9}$	17	4	5	2	3	2
$1 \times 10^{-9}$	6	3	2	2	2	2
Control	2					

1 = 4-methyl-5-hydroxyethyl thiazole

1 W = 4-methyl-5-hydroxyethyl thiazole

1 M = 4-methyl-5-hydroxyethyl thiazole

1 B = 4-methyl-5-hydroxyethyl thiazole

I G Farbenindustrie

Winthrop

Merck

Buchman (supplied by Dr James Bonner)

2 = 4-methyl-5-hydroxyethyl thiazole benzoic acid ester I G Farbenindustrie

tests showed three of the thiazoles to be seriously contaminated to different extents with pyrimidines or substances capable of acting in that capacity. Contaminating substances in the fourth thiazole were of sufficiently low concentration to be detectable only when used in excessively high concentrations, concentrations up to  $10^{-5}$  M failed to provide a satisfactory source of growth factors for *Prototheca*.

*Growth of Prototheca on Mixtures of the Natural Thiazole and Pyrimidine Components*—Experiments were carried out to determine the ability of *Prototheca* to grow in a series of media containing graded concentrations of mixtures of the purest thiazole and one of the natural pyrimidine preparations. The results of one experiment are summarized in Table IV. They show unequivocally that *Prototheca zopfii* is able to utilize a combination of the two com-

ponents in place of the whole thiamin molecule and that the components are required in equimolar proportions. The cell yield is determined by the component of the thiamin molecule that is present in the smaller amount.

The data obtained in these experiments give rise to some further comments. Both in the absence and in the presence of very low concentrations of thiazole the growth of *Prototheca* appears to be due to some extent to the amount of pyrimidine present. This suggests the presence of a limited supply of thiazole in either the medium, the inoculum, or as a contaminant of the pyrimidine. The presence of thiazole as an impurity of the pyrimidine should have resulted in increased growth in the excessively high concentrations used to test this component alone and, therefore, can be ruled out.

TABLE IV

Cell Yield in  $\text{Mm}^3$  per 10 ml of *Prototheca* Cultures Grown in the Presence of Different Concentrations of Mixtures of the Purest Thiazole and Pyrimidine

Molar concentration			Pyrimidine 3B								
			0	$\frac{1}{10} \times 10^{-7}$	$\frac{1}{3} \times 10^{-7}$	$\frac{1}{10} \times 10^{-6}$	$\frac{1}{3} \times 10^{-6}$	$\frac{1}{10} \times 10^{-5}$	$\frac{1}{3} \times 10^{-5}$	$\frac{1}{10} \times 10^{-4}$	$\frac{1}{3} \times 10^{-4}$
Thiazole 1B	$3 \times 10^{-7}$	2	3	5	12	22	42	92	92	94	94
	$1 \times 10^{-7}$	2	3	5	12	22	42	100	100	96	96
	$3 \times 10^{-8}$	2	3	5	12	21	44	92	92	94	94
	$1 \times 10^{-8}$	2	3	5	12	21	41	54	54	48	48
	$3 \times 10^{-9}$	2	3	5	10	17	22	22	22	22	22
	$1 \times 10^{-9}$	2	3	4	10	14	15	14	14	15	15
	$3 \times 10^{-10}$	2	3	4	10	12	11	11	12	12	12
	$1 \times 10^{-10}$	2	3	4	8	11	12	11	11	11	11
	0	2	3	4	8	9	10	9	11	10	10

The occurrence in nature of thiazole unaccompanied by an equivalent quantity of pyrimidine is apparently so rare that the chemicals used in the basal medium would seem most unlikely as a source of thiazole contamination. If thiazole were introduced with the inoculum it can be inferred that the cells used for this purpose must have contained an excess of thiazole. Special experiments, however, to test the storage of thiazole by *Prototheca* gave negative results.

The higher concentrations of the mixtures allow a total cell yield closely approximating the maximum growth obtainable in cultures growing in media containing the complete vitamin or yeast autolyzate. A number of experiments have shown that maximum cell yield is obtained at a concentration approximately  $3 \times 10^{-8}$  M for each component of the thiamin molecule. It is interesting to note that this is about one-tenth of the concentration necessary when the whole molecule is used. This observation is in line with that of Schopfer who found *Phycomyces blakesleeanus* to require approximately twice as much thia



min as a mixture of the two components in order to give comparable maximum yields

Since the alga cannot grow unless supplied with both pyrimidine and thiazole, *Prototheca zopfii* represents another member of the previously mentioned group (b)

#### SUMMARY

Barker's study on the nutritive requirements of *Prototheca zopfii* indicated that this colorless alga fails to grow in the absence of small amounts of yeast extract. A study of the growth factor requirements of *Prototheca* has shown that the active constituent of yeast extract necessary for the growth of this organism is thiamin (vitamin B<sub>1</sub>). Thiamin can fully replace the complex yeast material and allows, in the basal medium used, a maximum cell yield in concentrations of  $1-3 \times 10^{-7}$  M.

Thiamin as such, however, is not essential for the growth of *Prototheca zopfii*. The alga can develop equally well if supplied with both the thiazole and pyrimidine constituents of this vitamin. These appear to be needed in equimolar proportions. Maximum cell yield is obtained with  $3 \times 10^{-8}$  M concentrations of the two components.

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# STUDIES ON THE METABOLISM OF THE COLORLESS ALGA PROTOTHECA ZOPFII

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## INTRODUCTION

The first studies dealing with the physiology of the colorless alga *Prototheca zopfii* were those of Barker (1, 2) who demonstrated that the metabolism of this organism was essentially of an oxidative nature. He found that while it was capable of carrying on an anaerobic metabolism in that it could ferment glucose quantitatively to lactic acid, it was totally unable to develop under strictly anaerobic conditions. In this respect its metabolism may be compared with that of mammalian muscle tissue.

Barker made a detailed study of the metabolism of this alga in regard to its nutritional requirements for growth and to its ability to utilize a great variety of simple carbon compounds as the sole substrate.

Of the carbohydrates tested, only the monosaccharides were utilized by *Prototheca*. All of the fatty acids, with the exception of formic and isovaleric acid, appeared adequate as carbon sources, as did many of the alcohols and ketones. None of the nitrogen-containing compounds (glycine, asparagine, glucosamine, ethylamine, or yeast autolysate) was found to serve as a carbon source. The most surprising result was the fact that not a single substituted or dicarboxylic acid tested by Barker would serve as a utilizable substrate.

The study of the carbon nutrition was approached experimentally in two ways. Culture experiments in which the substance under investigation constituted the main carbon source of the medium showed what compounds could serve for growth. The effect of the addition of various organic substrates upon the oxygen consumption by suspensions of non-growing cells was studied with the manometric technique of Warburg-Barcroft.

In all cases of the oxidation of utilizable compounds, Barker was able to express the relationship between the quantity of substrate, oxygen, and carbon dioxide participating in the reaction in terms of a balanced chemical equation having simple stoichiometric relations. This relationship showed conclusively that those compounds which are attacked by *Prototheca* are not oxidized completely to carbon dioxide and water, but that a considerable fraction from 50 to 80 per cent, is converted into a primary assimilation product having an over all composition corresponding to that of a carbohydrate which is stored in the cells probably as glycogen. Barker's experiments showed that the process of assimilation of simple organic substrates by this alga proceeds

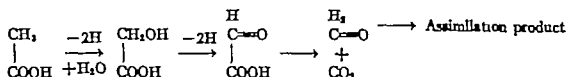
in two distinct stages. The first he found to consist of a very rapid oxidative conversion of the substrate into carbon dioxide and the stored material. The second stage comprises a slow decomposition of this primary assimilation product and its subsequent transformation into many different organic substances which make up the cell material.

This was the first convincing demonstration that, during the respiration of simple organic compounds by non-proliferating organisms, assimilation processes occur to an unexpectedly large extent. That a large oxidative assimilation is not restricted to the metabolism of a colorless alga was soon evidenced by the studies of Giesberger (3) on various *Spirillum* species and by Clifton (4, 5) on *Pseudomonas calcoacetica* and *Escherichia coli*.

Since the oxidation of such simple compounds as acetic acid by *Prototheca* resulted in so extensive a synthesis of carbohydrate-like materials, it suggested the possibility of an experimental approach to the problem of the mechanism of synthetic processes in general. The stoichiometric relationship seemed to indicate that the substrate would be partially oxidized, giving rise to intermediate products from which the synthesis to carbohydrate could proceed directly. In that case, a study of the behavior of the various organic compounds that could be postulated as being intermediate products in the synthesis of carbohydrate from acetic acid should reveal the general pathway of the metabolic reactions involved in the biochemical synthesis. This would appear to be a most fruitful approach, particularly in view of the fact that a vast number of studies have clearly demonstrated that the production of carbohydrate is one of the most important aspects of photosynthesis.

*Prototheca* is a member of the family Oocystaceae, order Chlorococcales, class Chlorophyceae (Chlorophyta), and represents an alga devoid of chlorophyll, and hence unable to produce organic cell materials from carbon dioxide as the sole carbon source. Nevertheless, in a primary assimilatory process such as is characteristic of the metabolism of *Prototheca*, the synthesis of carbohydrate from a simple organic compound shows a certain similarity to the photosynthetic reaction. Moreover, the great economy of carbon assimilation is not entirely restricted to photosynthesis, as is evidenced by the fact that Barker found *Prototheca* capable of assimilating such a large percentage of the carbon of a single substrate. One might expect the further conversions of the primary assimilatory product into numerous cell materials to proceed by much the same types of mechanism in both *Prototheca* and in the green plants, so that a detailed study of the metabolism of the former would ultimately aid in understanding that of the latter. Finally, heterotrophic organisms in general carry out synthetic reactions of various sorts. In view of the well established similarity of biochemical mechanisms in the most divergent types of organisms, a study of carbohydrate synthesis from acetate by *Prototheca* should be of decided value in contributing to a general clarification of such syntheses.

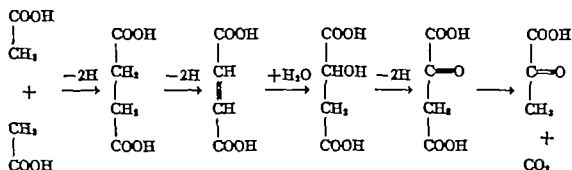
However promising the outlook, Barker's experiments appeared, at that time, to lead up a blind alley. This can best be appreciated by considering the oxidative metabolism of *Prototheca* in the presence of acetate. Two main pathways for the decomposition of this metabolite can be postulated. One would be through successive oxidations to glycolic and glyoxylic acids and its subsequent decarboxylation (Bernauer (6))



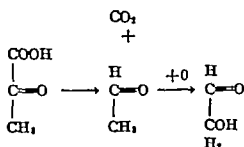
Synthesis of carbohydrate could then take place from the formaldehyde," more or less in accordance with von Bayer's concept of carbohydrate formation in photosynthesis

If *Prototheca* were to oxidize acetate in this manner it should follow that both glycolic acid and glyoxylic acid could be metabolized. Barker was forced to rule out this series of reactions, however, since *Prototheca* was incapable of oxidizing either intermediate.

The second manner in which acetate could be oxidized proceeds by way of succinic, fumaric, and oxalacetic acids, followed by decarboxylation to pyruvic acid (Thunberg (7))



The further fate of pyruvic acid could be postulated to lead, through a second decarboxylation, to acetaldehyde from which by oxidation to glycol aldehyde, carbohydrate might be formed by condensation



This scheme too, would satisfy the experimental values for the relationship between acetate used, oxygen consumed, and carbon dioxide produced. But

this series proved no more tenable than did the first, for the intermediates here involved were likewise not metabolized when tested by Barker -

The identification of thiamin as the growth factor for *Prototheca* (8) made it possible to investigate its specific function in the oxidative metabolism of this organism. In the course of this work a number of new facts were discovered which gradually led to a skeptical attitude with respect to the general validity of some of Barker's findings. A reinvestigation of certain phases of his work was then undertaken which resulted in a much more satisfactory picture of the metabolism of the experimental organism. This, in turn, made it possible to carry out some preliminary experiments in connection with the assimilation problem proper.

### *Material and Methods*

*Organism*—The strain of *Prototheca zopfii* used in these investigations was No. 7322, one of several maintained in the pure culture collection of the Hopkins Marine Station, and is the same strain as that used in the studies on the growth factor requirements of this organism (8).

*Medium and Methods of Culture*—Cultures of the organism were maintained on yeast agar containing 2 per cent dextrose.

"Normal" or vitamin-sufficient cells for use in making manometric measurements were grown on plates of the yeast dextrose agar medium incubated at 30°C for 48 hours. The cells were washed once or twice by centrifuging and resuspended in sterile tap water at pH 7.0, or in M/15 phosphate buffers of the desired pH.

To obtain thiamin-deficient cells it is necessary to grow the organism in a medium in which thiamin is the limiting factor. Such cells were obtained by using a glycerol mineral medium (8) to which thiamin was added in sufficient amounts to allow good growth with limiting concentrations of the vitamin. The cells were grown in several rotating bottles, each containing 25 ml. volumes of glycerol mineral medium to which thiamin had been added. At the end of a 6 day period of incubation at 30°C the cultures were pooled, centrifuged, washed once or twice, and resuspended in neutral sterile tap water, or in M/15 phosphate buffers, in a concentration suitable for use in making manometric measurements.

### FUNCTION OF THIAMIN IN THE METABOLISM OF PROTOTHECA ZOPFII

Thiamin has been found to be essential for the normal development of *Prototheca* (8). Therefore the hypothesis that a growth factor or a vitamin represents the functional (active or prosthetic) group of an enzyme without which normal metabolism cannot proceed, leads to the assumption that the alga needs carboxylase and uses this enzyme in its metabolism but is unable to synthesize carboxylase unless supplied with thiamin or its component parts.

It was generally held, at the time the present work was undertaken, that the sole function of carboxylase was to catalyze the decarboxylation of  $\alpha$ -keto acids. Furthermore, since the only known connection of thiamin with enzymes was its occurrence in carboxylase, it seemed logical to conclude that the de-

carboxylation of  $\alpha$ -keto acids formed an integral part of the metabolism of *Prototheca zopfii*.

*Prototheca* is capable of using sugars as a substrate. From the accumulated data on the sugar metabolism of various organisms it was logical to assume pyruvic acid to be an intermediate substance in the decomposition of sugar. Therefore carboxylase, and hence thiamin, could be expected to be needed in the metabolism of this alga. A serious difficulty was presented, however, by the fact that Barker had claimed *Prototheca* to be incapable of decomposing pyruvic acid. Consequently, Barker's experiments on the utilization of pyruvic acid by *Prototheca* were repeated.

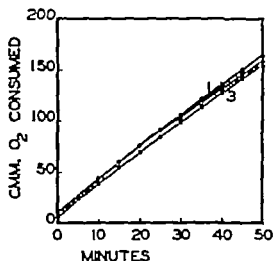


FIG 1 Oxidation of pyruvate at pH 7.0 by non-deficient cells of *Prototheca* (1) autorespiration (2) 0.01 mM Na pyruvate (3) 0.01 mM Na pyruvate plus 10  $\gamma$  thiamin

The oxygen consumption of 2.0 ml. volumes of normal cells in neutral tap water was measured by the manometric technique of Warburg Barcroft, in vessels containing KOH in the center well. In the absence of an added substrate which the cells are capable of utilizing the rate of oxygen consumption by such suspensions of non-proliferating cells is relatively low and represents the rate of oxidation of cellular materials, such as reserve carbohydrates. The addition of a utilizable substrate greatly increases the rate of oxygen consumption (see also Barker (2)). Numerous experiments demonstrated that the addition of sodium pyruvate to such suspensions did not result in an increase in the rate of oxygen utilization. Even the addition of thiamin did not cause an acceleration of oxygen uptake. Fig 1 represents the results obtained in one typical case.

The results were in complete agreement with the experiments reported by Barker. As a consequence of these unequivocal findings, Barker's conclusion that *Prototheca* was unable to decompose pyruvic acid was believed to be correct.

In view of the recognized function of carboxylase, it was difficult to understand why *Prototheca* needed thiamin as a growth factor and yet was unable

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to decompose pyruvic acid. This strongly indicated that in the case of *Prototheca* thiamin might be used not for the synthesis of carboxylase, but for the synthesis of an enzyme concerned in the decomposition of organic compounds other than  $\alpha$ -keto acids. The most characteristic metabolites for *Prototheca* are the unsubstituted fatty acids, especially acetic, as is attested by the abundant development of this organism in vinegar casks (Janke (9)). This natural occurrence of the alga indicates that acetic acid is a suitable enrichment substrate for *Prototheca*. Furthermore, the careful and extensive studies of Barker had shown that *Prototheca* was unable to utilize any but the fatty acids. Therefore, it seemed possible that thiamin might function in the decomposition of the fatty acids, and in particular in the oxidation of acetic acid. Consequently experiments were designed to determine whether thiamin functioned in the oxidation of fatty acids by *Prototheca*.

The method of approach was based on the technique developed by Lwoff (10) in his investigations on the rôle of blood in the nutrition of trypanosomes and later utilized by Hills (11) in his studies on the part played by thiamin, a growth factor for *Staphylococcus aureus*, in the metabolism of this organism.

Hills showed that staphylococci, grown with minimal amounts of thiamin, consumed oxygen in the presence of pyruvate as a substrate at a very low rate. The rate of oxygen consumption was immediately increased by the addition of minute amounts of thiamin. Cells grown with optimum amounts of thiamin were capable of a rapid decomposition of pyruvate and their oxygen consumption was not affected by the addition of the vitamin. These experiments made it clear that the oxidation of pyruvate by *Staphylococcus aureus* requires an enzyme which the organism can rapidly synthesize from thiamin. The fact that the anaerobic decomposition (decarboxylation) of pyruvic acid by "thiamin-deficient" cells was also greatly and immediately increased by the addition of thiamin to the cell suspension, showed that the main, if not only, function of the vitamin, in the metabolism of *Staphylococcus aureus*, is its conversion into carboxylase.

The above examples illustrate what could be expected from an application of Lwoff's "starvation" methodology to a study of the metabolism of *Prototheca*. Those substrates, for which a special thiamin-containing enzyme is required, would be decomposed slowly by cells that had been grown in media deficient in this vitamin. The addition of small amounts of thiamin to suspensions of such deficient cells should result in an immediate and rapid synthesis of the limiting enzyme system with a subsequent increase in the rate of utilization of the substrate.

#### *Experiments with Thiamin-Deficient Cells*

To determine if thiamin functioned in the oxidation of fatty acids by *Prototheca* the following experiment was carried out

Thiamin-deficient cells were obtained by growing the organism in glycerol mineral medium to which  $1 \times 10^{-4}$  M thiamin had been added. Two ml samples of the non-proliferating cells resuspended in neutral tap water were placed in the vessels of Warburg Barcroft manometers. Each vessel contained KOH in the center well and a gas phase of air. Ten  $\mu$ g of thiamin were added to the suspension in each of two vessels. Measurement of oxygen consumption in the absence of added substrate showed the cells without added thiamin to have a low rate of oxygen uptake. On the other hand the cells supplied with thiamin showed a rate of oxygen utilization approximately twice that of the starved cells. This difference in autorepiration indicates that the addition of thiamin allows the cells to utilize some of their stored materials more rapidly, suggesting that the lack of the vitamin restricted the metabolism of these substances.

The addition of 0.01 mM of sodium acetate caused a rapid and nearly identical increase in oxygen consumption by the cells deficient in thiamin and by those to which thiamin had been added as well. In this case, therefore, thiamin had no effect whatever on the oxidation of acetate.

The addition of 0.01 mM of dextrose presented an entirely different picture. The thiamin-deficient cells consumed oxygen at a very low rate; the quantity utilized during the first hour was exactly the same as in the control. The extra oxygen consumption in the suspension containing sugar, which began at that time, increased slowly thereafter. The behavior of deficient cells was plainly different from that of normal cells in the presence of dextrose. Cells having access to thiamin showed an immediate increase in oxygen consumption in response to the addition of dextrose. The marked difference in rate of decomposition of dextrose by the deficient cells with and without added thiamin clearly indicated that thiamin is essential to *Prototheca* in its metabolism of dextrose. The results of a representative experiment showing the effect of thiamin on the oxidation of acetate and of dextrose are presented in Fig. 2.

Apparently *Prototheca* could oxidize a representative of the fatty acids without benefit of thiamin, but it did need this substance, or its components, for growth and for the utilization of a sugar. The failure of thiamin to affect the oxidation of acetic acid indicated that there was no reason to ascribe to it a function in the metabolism of fatty acids. Its pronounced influence on sugar metabolism supported the possible relation of thiamin to the decomposition of pyruvic acid. It was almost certain that this  $\alpha$  keto acid would occur as an intermediate substance in the degradation of sugar by *Prototheca zoffii*. The strongest support for this contention was the extensive production of lactic acid from glucose under anaerobic conditions (Barker (1)). The entire body of evidence amassed by Emden, Meyerhof, and others (12) made it reckless to suggest that the formation of this hydroxy acid would not proceed, in the case of *Prototheca*, by the well established mechanism of the reduction of pyruvic acid. In sharp contrast with these theoretical deductions was the experimental evidence, showing that pyruvate was not metabolized by *Prototheca*.



*Experiments on the Effect of pH on the Decomposition of Pyruvic Acid*

In all cases, determinations of the ability of *Prototheca zopfii* to utilize a given substrate had been carried out in neutral solutions. There is much evidence to show that cells are more freely permeable to undissociated molecules than to ions.

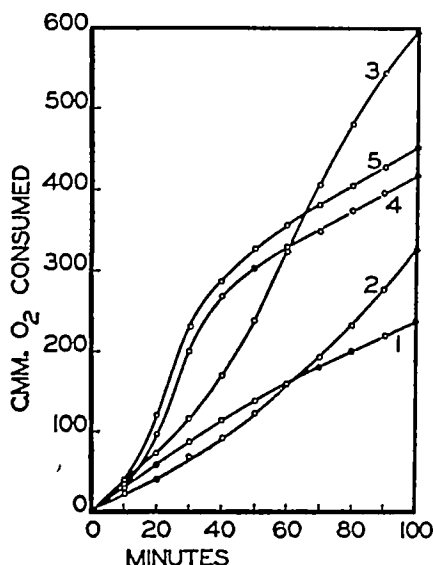


FIG 2

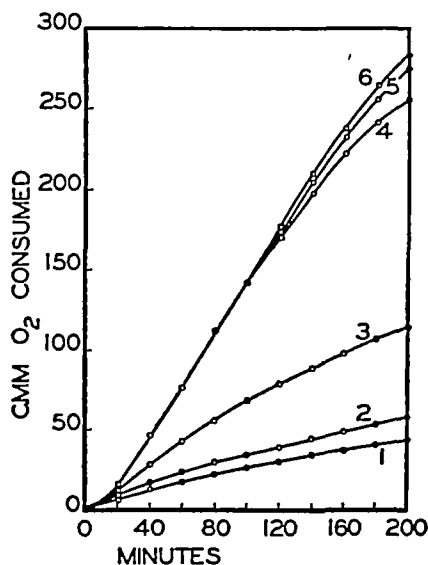


FIG 3

FIG 2 Effect of thiamin on oxidation of dextrose and acetate by vitamin-deficient cells of *Prototheca* at pH 7.0 (1) autorespiration, (2) 0.01 mM dextrose, (3) 0.01 mM dextrose plus 10  $\gamma$  thiamin, (4) 0.01 mM Na acetate, (5) 0.01 mM Na acetate plus 10  $\gamma$  thiamin

FIG 3 Effect of pH on pyruvic acid oxidation (1) autorespiration at pH 4.0, (2) 0.01 mM pyruvic acid at pH 6.0 to 5.5, (3) at pH 5.5 to 4.5, (4) at pH 4.5 to 4.0, (5) at pH 4.0 to 3.5, (6) at pH 3.5 to 3.0

The work of Osterhout, Collander, and others has shown that in a neutral environment weakly dissociating acids and bases penetrate cells more rapidly than do strongly dissociating ones. Conditions that suppress the dissociation of a substance have a tendency to increase its penetration. There are indications in the literature that many organisms are unable to metabolize strong acids except in an acid environment. A striking example of this phenomenon is furnished by the photochemical nitrate reduction carried out by the green alga, *Chlorella*. Warburg and Negelein (13) found this reaction to take place only in solutions containing undissociated nitric acid. The anaerobic decomposition of pyruvic acid by yeast has also been shown to proceed most rapidly in an acid medium (14). Pyruvate is decomposed by cell-free yeast juice at a pH of about 6.0. Living yeast cells, however, fail to cause any appreciable decomposition of the keto acid until the acidity of the suspending medium is increased.

to a value below pH 4.0. Such behavior may be explained as a result of the nature of the cellular membrane of certain cells which allows acids to penetrate only in the form of undissociated molecules.

Therefore experiments were conducted to test the possibility that pyruvic acid might be attacked when the suspension liquid was maintained at an acid reaction.

Vitamin non-deficient cells were obtained in the usual manner and resuspended in sterile tap water at a pH of 7.0. One-half ml. of the suspension, containing  $12 \text{ mm.}^3$  of cells, was measured into each of six Warburg vessels containing 1.5 ml. of a series of phosphate solutions at pH values ranging from pH 6.0 to 3.5. Each vessel contained NaOH in the center well and air as the gas phase. Autorepiration, determined over a period of 90 minutes, was quite similar throughout the range of hydrogen ion concentrations used. The lower pH values, however, did have a slight stimulatory effect on the rate of oxygen consumption, the cells at pH 3.5 using  $43 \text{ mm.}^3$  of oxygen during the initial 90 minute period as against  $35 \text{ mm.}^3$  at pH 6.0.

The addition of 0.01 m $\mu$  of pyruvic acid to the suspension of cells at pH 6.0 lowered the pH to 5.5 and caused a very slight initial increase of oxygen uptake which soon returned to a rate identical with that for the autorepiration ( $13 \text{ mm.}^3$  per 50 minutes). At this stage the pH had risen to 5.7 as a result of the decomposition of a small amount of added pyruvic acid. At pH 5.5 the addition of the same amount of acid caused an increase in acidity to pH 4.5 with a subsequent initial rate of oxygen consumption of  $38 \text{ mm.}^3$  per 50 minutes which gradually fell off to a rate of  $24 \text{ mm.}^3$ . Again at this point, the decomposition of a portion of the pyruvic acid had resulted in a decrease in acidity of the suspension, pH determinations showed it to be 5.2. The addition of the keto acid to the suspensions of organisms at pH 4.5, 4.0, and 3.5, now lowered to pH 4.0, 3.5 and 3.0 respectively presented a distinctly different picture. In these three cases the rate of oxygen utilization immediately rose to  $80 \text{ mm.}^3$  per 50 minutes. This high rate was maintained until the pyruvic acid had been decomposed. Final pH determinations of these three suspensions showed that their acidity had returned to the initial values. The oxygen consumption for each suspension, from the time the pyruvic acid was added is shown in Fig. 3.

Since the metabolism of pyruvic acid proceeded in nearly an identical manner at pH 4.0, 3.5 and 3.0 the highest value was chosen for use in all subsequent experiments in order to avoid any possible injury to the cells by an environment too strongly acid. Although Barker (1) reported an increase in hydrogen ion concentration to have an adverse effect on the rate of dextrose decomposition by growing cultures of *Prototheca*, further tests have shown that at pH 5.0 at least, the decomposition of dextrose by non-proliferating cells is certainly not inhibited but rather that the acid environment exerts a stimulatory effect.

This experiment was the first to demonstrate that *Prototheca* does possess enzyme systems capable of decomposing pyruvic acid. From the data recorded in Fig. 3, it is seen that a hydrogen ion concentration greater than that corresponding to pH 4.5 is necessary in order that pyruvic acid may be made available to the intracellular enzyme systems.

*Effect of Thiamin on Pyruvate Decomposition*

To determine whether thiamin is needed in the metabolism of *Prototheca* in the rôle ascribed to carboxylase, vitamin-deficient cells, with and without added thiamin, were tested for their ability to decompose pyruvic acid in an acid environment

Deficient cells grown in glycerol mineral medium containing  $1 \times 10^{-8}$  M thiamin were centrifuged, washed twice in M/15 primary phosphate solution adjusted to pH 4.0 by the addition of  $\text{H}_2\text{SO}_4$ , and resuspended in the "buffer" in a concentration suitable for use in Warburg measurements. Two ml of the suspension, containing  $32 \text{ mm}^3$  of cells, were introduced in each of the vessels and the rate of oxygen consumption measured. The first vessel received no added substrate and, therefore, its rate of oxygen uptake is a measurement of the autorepiration of stored cellular materials. The cells in the second vessel received 0.01 mM of pyruvic acid. With the addition of the acid the rate of oxygen consumption was increased, indicating that the vitamin-deficient cells were able to decompose pyruvic acid. To the suspension of cells in the third vessel were added 10  $\mu\text{g}$  of thiamin. The addition of the vitamin to the deficient cells caused an immediate but slight increase in the rate of autorepiration. Addition of 0.01 mM of pyruvic acid to the cells now supplied with thiamin, caused a rate of oxygen uptake 2.5 times the maximum obtainable with the vitamin-deficient cells to which no thiamin was added. Suspensions of cells treated in a manner identical with that of deficient cells, except that they had been grown in a medium containing an optimum amount ( $1 \times 10^{-6}$  M) of thiamin, were able to decompose pyruvic acid at a high rate without added vitamin. The vitamin-sufficient cells showed no increase in rate of oxygen consumption on the addition of the same amount of thiamin which caused a 2.5-fold increase in the rate with the deficient cells. The data obtained in one representative experiment are presented in Fig. 4.

Extensive investigations of the effect of thiamin on decomposition of pyruvic acid by suspensions of non-proliferating, vitamin-deficient cells have shown that the addition of the vitamin in general causes a 2.0 to 3.0-fold increase in the rate of oxygen consumption. The percentage of increase is dependent on the degree of vitamin deficiency and on the age of the "insufficient" cells.

Organisms grown in media containing  $1 \times 10^{-8}$  M vitamin  $\text{B}_1$  tend to show a greater increase in rate of oxygen consumption on the addition of thiamin, while respiring pyruvic acid, than do cells grown in  $3 \times 10^{-8}$  M vitamin  $\text{B}_1$ . Likewise, cells grown for 96 hours in media containing  $1 \times 10^{-8}$  M vitamin  $\text{B}_1$  tend to show a greater response than do cells grown in similar media for 72 hours. It is assumed that the older cells are more vitamin "starved" than are the younger cells, since the older cultures contain more cells per unit volume and, therefore, the available vitamin has been distributed to a larger number of organisms. Numerous tests have shown the addition of 10  $\mu\text{g}$  of thiamin to 2.0 ml suspensions of vitamin-deficient cells to provide an arbitrary but entirely adequate amount of the vitamin to insure maximum rates of metabolism under all conditions of thiamin deficiency of the cells.

*Evidence for the Occurrence of Pyruvic Acid As an Intermediate Product in the Metabolism of Prototheca*

With the finding that *Prototheca zopfii* can utilize pyruvic acid the apparent discrepancies in the metabolism and growth requirements of the alga appeared to be solved. Thiamin was shown to immediately affect the metabolism of

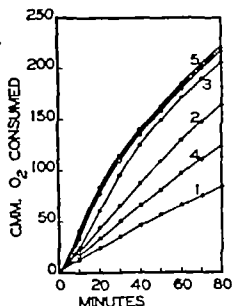


FIG 4

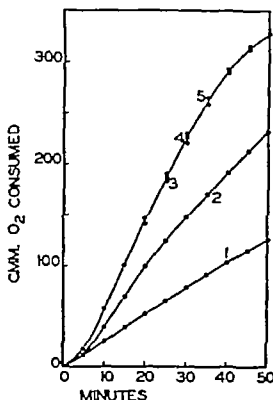


FIG 5

FIG 4 Effect of thiamin on pyruvic acid oxidation (1) autorespiration of deficient cells, (2) deficient cells plus 0.01 mM pyruvic acid, (3) deficient cells plus 0.01 mM pyruvic acid plus 10  $\gamma$  thiamin, (4) autorespiration of non-deficient cells (5) non-deficient cells plus 0.01 mM pyruvic acid, (6) non-deficient cells plus 0.01 mM pyruvic acid plus 10  $\gamma$  thiamin.

FIG 5 Effect of pH on lactic acid decomposition (1) autorespiration (2) 0.01 mM lactic acid at pH 6.0 (3) at pH 5.0 (4) at pH 4.5 (5) at pH 4.0

the alga in the presence of sugar and pyruvic acid, but not in the presence of acetate. Therefore the conservative ideas of the function of the vitamin, or its components, as building blocks for the carboxylase, appear applicable in the case of *Prototheca*.

Lactic acid was tested and found to be attacked by non proliferating cells of *Prototheca*. This hydroxy acid also was decomposed by the cells only in an acid environment.

Lactic acid ( $K_a=0.031$ ) is not so strong an acid as is pyruvic ( $K_a=0.56$ ), and consequently is not so highly dissociated in aqueous solutions. Therefore it would follow

that *Prototheca* suspensions might decompose lactic acid in an environment having a hydrogen ion concentration lower than that required to permit the decomposition of pyruvic acid. The data contained in Fig. 5 indicate that such might be the case. A hydrogen ion concentration corresponding to pH 5.0 will permit a maximum rate of oxygen consumption with lactic acid as a substrate while a pH below 4.5 is necessary for the maximum rate of oxidation of pyruvic acid.

The rate of oxygen utilization of thiamin-deficient cells metabolizing lactic acid could also be increased by the addition of thiamin although the stimulatory effect of the vitamin was not so great as in the case of pyruvic acid. While the addition of thiamin caused a 2.0 to 3.0-fold increase in the rate of pyruvate decomposition, the rate for lactic acid decomposition was increased about 1.4 times. This difference finds a ready explanation in that the decomposition of lactic acid, with pyruvic acid as an intermediate, requires an oxygen uptake for the conversion of the hydroxy to the keto acid. This reaction should be unaffected by vitamin B<sub>1</sub> (carboxylase). The oxygen utilized in this conversion, however, would be included in the rate of oxygen consumption measured. Therefore, the portion of the oxygen consumption which could be expected to be directly influenced by carboxylase would be much less in the decomposition of lactic acid than in the decomposition of pyruvic acid.

The assumption that thiamin functions in the rôle of carboxylase in the normal metabolism of *Prototheca zopfii* is further substantiated by observations on cultures of the alga growing in glycerol media. Pyruvic acid was found to accumulate in the culture medium containing insufficient amounts of the vitamin, whereas not a trace of this substance could be detected in cultures that had grown in the presence of an optimum supply of the growth factor. This is in line with the observations of Platt and Lu (15) and others that pyruvic acid accumulates in tissues and body fluids of animals deprived of vitamin B<sub>1</sub> and also with the finding of Peters (16, 17) that avitaminotic brain tissues of pigeons oxidize pyruvic acid at a subnormal rate.

The experimental evidence that pyruvic acid accumulates in glycerol cultures growing in the presence of suboptimal concentrations of thiamin clearly indicates the formation of the keto acid as an intermediate product in the oxidation of glycerol and demonstrates the difficulty of vitamin B<sub>1</sub>-deficient cultures in disposing of pyruvic acid.

#### *Effect of Thiamin on the Metabolism of Acetate by Prototheca*

Up to this point, studies on the metabolism of vitamin-deficient cells of *Prototheca zopfii* have shown the oxidation of glucose, pyruvic acid, lactic acid, and glycerol to be markedly increased by the addition of small amounts of vitamin B<sub>1</sub>. Since pyruvic acid may be assumed to occur as an intermediate product in the oxidation of all these compounds, and has been demonstrated to accumulate during the "oxidation" of glycerol by thiamin-starved cells,

the results so far presented do not offer any indication that thiamin participates in the decomposition of substances other than  $\alpha$ -keto acids. This is in complete harmony with the hitherto accepted function of carboxylase.

However, later experiments on the oxidation of acetate by non proliferating, vitamin-deficient cells grown in the presence of  $1 \times 10^{-8}$  M thiamin showed the rate of oxidation of this substrate to be materially accelerated by the addition of thiamin. The results of five experiments, presented in Table I, appear contradictory to previous findings (see Fig. 2). The cells tested in the earlier experiments had been grown in media containing  $1 \times 10^{-7}$  M thiamin and, therefore, cannot be considered to have been so deficient as the cells which were produced in the presence of  $1 \times 10^{-8}$  M thiamin. It would appear, therefore, that a vitamin deficiency is manifest first in the metabolism of

TABLE I

*Effect of Thiamin on the Oxidation of Acetate by Suspensions of Thiamin Deficient, ( $1 \times 10^{-8}$  M), Cells of *Prothotheca zopfi**

Age of culture	O <sub>2</sub> utilization		Increase
	With thiamin	Without thiamin	
hrs.	mm <sup>3</sup> per 50 min.	mm <sup>3</sup> per 50 min.	per cent
72	117	85	138
72	137	95	144
90	137	87	157
96	100	65	154
96	75	47	160

pyruvic acid, and only later with acetate. Also it should be stated that the deficiency is more pronounced in the metabolism of pyruvic acid, a two- to three-fold stimulation was found with pyruvic acid as a substrate as against an average 1.5-fold increase with acetate.

The somewhat similar stimulatory effect of thiamin on vitamin-deficient cells oxidizing lactic acid was interpreted on the basis that pyruvic acid occurs as an intermediate product in the decomposition of the hydroxy acid and that, therefore, thiamin functions in the oxidation of the keto acid. Is it probable or possible that a similar explanation may be found to interpret the results obtained with acetate?

The mechanism of the oxidation of acetic acid is still unknown. However it is not improbable that some  $\alpha$ -keto acid might be involved as an intermediate product in the decomposition of this simple fatty acid. From a consideration of the schemes for oxidation of acetate proposed in the introduction, either pyruvic acid or glyoxylic acid can be postulated to appear as intermediate products. In that event the effect of thiamin on acetate oxidation would be

similar to its function in the oxidation of lactate, glycerol, or dextrose. That is, thiamin would act in a secondary rôle.

The observation that thiamin can effect the oxidation of acetic acid by *Prototheca* is important in view of the demonstration by Quastel and Webley (18, 19) that vitamin B<sub>1</sub> appears to be essential for the oxidation of acetic acid by an unknown species of bacterium<sup>1</sup>. This organism, when grown on media containing suboptimal amounts of thiamin, responded strongly to additions of vitamin B<sub>1</sub>. This stimulation was found to be particularly pronounced if the vitamin was added in the presence of magnesium and potassium ions (Mg<sup>++</sup> and K<sup>+</sup>).

On the basis of their results, Quastel and Webley have given an involved explanation of this combined vitamin and metal ion effect without, apparently, envisaging the possibility that the response might simply be due to thiamin functioning in the decomposition of intermediate products in the nature of  $\alpha$ -keto acids. At first sight their data might seem to effectively rule out the function of thiamin in relation to  $\alpha$ -keto acids. The stimulation of the rate of oxygen uptake for acetate appears to be much more pronounced than for pyruvate. While the rate of oxygen consumption in acetate oxidation is raised from 20.5 mm<sup>3</sup> of oxygen per hour per milligram of dried bacteria ( $Q_{O_2}$  20.5), to 63.1 by the addition of K, Mg, and thiamin, the oxygen uptake with pyruvate is increased only from  $Q_{O_2}$  19.9 to 37.1.

This difference in response, of course, is not a very solid argument against the participation of thiamin in the oxidation of pyruvate because the two substrates are *not* in the same "state of oxidation". As an example let us compare the effects obtained in the respiration of lactate and pyruvate. The maximum  $Q_{O_2}$  obtained on the addition of thiamin and metal ions was 37.1 for pyruvate oxidation, while for lactate the  $Q_{O_2}$  was 72. It is most significant that the addition of metal ions alone can increase the lactate  $Q_{O_2}$  from 35 to 53 while similar additions have no effect on the pyruvate  $Q_{O_2}$  which remains at about 20. On the other hand, the addition of thiamin alone raises the lactate  $Q_{O_2}$  from 35 to 52. The maximum increase in  $Q_{O_2}$  due to the addition of vitamin B<sub>1</sub> is therefore 17 for both lactate and pyruvate. Since Quastel and Webley have shown pyruvate to accumulate in suspensions of deficient cells fed lactate in the absence of thiamin, it may be asserted that the identical increase in  $Q_{O_2}$ , due solely to vitamin B<sub>1</sub> results from decomposition of pyruvate in both the lactate and pyruvate oxidation. A similar situation can be shown to exist in the case of succinate and fumarate.

In order to obtain vitamin-deficient cells Quastel and Webley grew their organisms on a deficient medium composed of Difco peptone, agar, and NaCl made up in distilled water and autoclaved for 1 hour at a pH of 9.0 to reduce the vitamin content. The

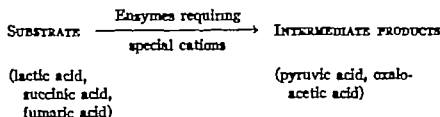
<sup>1</sup> Quastel and Webley claim the organism they used to be a propionic acid bacterium, *Bacterium acidipropionici*. This is most improbable, however, because it grows rapidly, aerobically, and is capable of growth in the absence of sugar or lactate as a substrate. Krebs and Eggleston (20) using the same strain, reported the organism incapable of producing propionic acid.

medium was then filtered through cotton and autoclaved again. As a result of this method of preparation it is obvious that the medium must have been deficient in most metals as well as in vitamin B<sub>1</sub>. Bacterial cells, grown in such an environment, consequently would themselves be deficient in various metals known to play an important rôle in the activity of a number of enzyme systems. That this was so is shown by the fact that if the deficient bacteria were incubated aerobically in the presence of Mg and K for a short time and afterwards thoroughly washed the oxidative powers of suspensions of such cells were increased by the addition of vitamin B<sub>1</sub> but not by the further addition of metal ions.

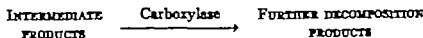
The picture of the combined vitamin and ion effect can best be presented by assuming that lactate, succinate, and fumarate must first be transformed into an oxidation product by reactions requiring the presence of metal ions rather than of thiamin. Following this the further fate of the intermediate products would involve reactions in which thiamin (carboxylase) participates. The first phase in the decomposition of lactate, succinate, and fumarate would then be slow if the cells had been grown in a medium with an inadequate supply of minerals, but the rate of this oxidation should be increased by the addition of the necessary cations alone. Only when the rate of formation of intermediate substances exceeds the capacity of the carboxylase system present would the addition of thiamin have a stimulatory effect.

If, on the other hand, the rate of production of intermediate substances were high, due to the presence of sufficient enzymatic capacity for the initial reaction the primary oxidation products would tend to accumulate in the presence of a limiting carboxylase supply. A case in point is the well known fact that pyruvic acid accumulates during the metabolism of sugar or lactate by thiamin-deficient organisms and tissues. The addition of thiamin would then cause an increase in metabolic rate, due exclusively to an effect on the second phase. This scheme may be illustrated by the following diagram.

#### Phase 1 Limited by cation supply



#### Phase 2 Limited by thiamin supply



In those cases where the rate of the first phase, although not maximal due to a cation deficiency, is nevertheless greater than the capacity of the enzymes operative in the second phase, the addition of either cations or of thiamin alone would cause an increase in the rate of oxygen consumption. However the increase in rate of oxygen consumption due to the addition of thiamin alone can only be due to an increased



capacity for carrying out the second phase. Since, in the case of lactic acid decomposition, the rate of the second phase of the reaction can be determined directly by a study of the metabolism of pyruvic acid, the idea here developed can be tested experimentally. Fortunately, the publication of Quastel and Webley contains all the necessary data for such a comparison. These data have been assembled in Table II.

It can be seen that the predictions agree with the actual measurements. When the rate of the first phase is not altered, the effect of the addition of thiamin is identical for the oxidation of both lactate and pyruvate. This is seen to be true at both a low and high rate of the first phase.

The same effects can be shown for succinic and fumaric acids, where oxaloacetic and pyruvic acids could be expected as intermediate products. The data for succinate and fumarate are recorded in Table III.

TABLE II

*Quastel and Webley's Data for the Oxidation of Pyruvic (PA) and Lactic (LA) Acids, Arranged to Show the Possibility of Interpreting the Oxidation of Lactic Acid to Occur in Two Phases—the Rate of the First Governed by the Presence of Cations (C), the Second by Thiamin (T)*

Addition to deficient cells	Reaction involving cations	Reaction involving thiamin	$Q_{O_2}$	Difference in $Q_{O_2}$ due to thiamin
PA	None	Slow	20	17
PA + C + T	None	Fast	37	
LA	Slow	Slow	35	17
LA + T	Slow	Fast	52	
LA + C	Fast	Slow	53	19
LA + C + T	Fast	Fast	72	

In the oxidation of succinic and fumaric acids by deficient cells the increase in rate of oxygen consumption caused by the addition of thiamin is not so high when cations are also present, *i.e.*, when phase 1 occurs at a rapid rate. A simple explanation for this discrepancy is based upon the assumption that the carboxylase system may now have become limiting. Although adequate to cope with the supply of intermediate products furnished by phase 1 when this proceeds slowly, it may not be supplemented sufficiently by thiamin addition to cause a commensurate decarboxylation of these products when phase 1 proceeds at a maximum rate. Here the comparison with the decomposition of pyruvic acid, involving a single decarboxylation, is not entirely justified because in the breakdown of succinic and fumaric acids *via* oxaloacetic acid two decarboxylation reactions occur.

As another possibility it may be assumed that the over-all metabolic rate in the presence of both cations and thiamin is actually limited by the capacity of the final oxygen-activating systems. A decision between these alternative hypotheses would rest upon the evaluation of the significance of the  $Q_{O_2}$  increments. The higher value

with fumarate favors the latter explanation, but the difference in increment for succinate and fumarate in the presence of cations is too small to make this a convincing argument.

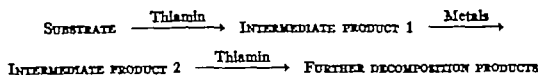
The stimulatory effect of thiamin and metal ions on the oxidation of acetate by Quastel and Webley's organism is different from that observed with lactate, pyruvate, succinate, and fumarate. In the case of the oxidation of this fatty acid, neither the cations nor thiamin alone permit the remarkable stimulation obtained when both are added together. This situation may be explained by assuming that a preliminary reaction, in which vitamin B<sub>1</sub> is involved, is required prior to the formation of a

TABLE III

*Quastel and Webley's Data for the Oxidation of Pyruvic (PA), Succinic (SA) and Fumaric (FA) Acids Arranged to Show the Possibility of Interpreting the Oxidation of Succinic and Fumaric Acid to Occur in Two Phases—the Rate of the First Governed by the Presence of Cations (C), the Second by Thiamin (T)*

Addition to deficient cells	Reaction involving cations	Reaction involving thiamin	Q <sub>01</sub>	Difference in Q <sub>02</sub> due to thiamin
PA	None	Slow	20	17
PA + C + T	None	Fast	37	
SA	Slow	Slow	30	19
SA + T	Slow	Fast	49	
SA + C	Fast	Slow	58	9
SA + C + T	Fast	Fast	67	
FA	Slow	Slow	28	17
FA + T	Slow	Fast	45	
FA + C	Fast	Slow	53	12
FA + C + T	Fast	Fast	65	

compound which can undergo dehydrogenation, a reaction for which metal ions are needed. The reactions involved in the oxidation of acetic acid may be represented by a series of steps.



It is improbable that such a preliminary step would involve a decarboxylation of acetic acid because biochemical decarboxylations have been observed exclusively with keto acids. Since carboxylase is likely to function in the carboxylation of acids as well as in their decarboxylation, the preliminary step involved in the oxidation of acetate by these bacteria might be the linking together of two acetate molecules to form acetoacetate. This reaction may be considered as equivalent to a carboxy

lation and hence might require carboxylase (*i.e.* thiamin). The consumption of oxygen in the decomposition of acetate by this scheme, should, therefore, be preceded by a step in which thiamin functions. The oxidation proper would involve the co-operation of the cation-requiring systems. In such a manner the observed effect of thiamin and cations on acetate oxidation by Quastel and Webley's organism could be readily harmonized with the concept that here, too, thiamin functions only as a building block of carboxylase.

*Theoretical Considerations on the Rôle of Thiamin in the Metabolism  
of Prototheca zopfii*

The experiments demonstrating a thiamin effect on the oxidation of acetate by *Prototheca zopfii* cannot as yet be interpreted in so detailed a manner. So far as is known, this alga has never been cultured in mineral-deficient media and, therefore, it is impossible to interpret the available data on the oxidation of acetate in the light of specific stepwise reactions. Whether thiamin has an *initial* or a *secondary* effect on the oxidation of this simple fatty acid by *Prototheca* must be left out of consideration for the present. At any rate, the function of thiamin in the oxidation of acetate need not be considered to be other than as a building block of carboxylase.

Krebs and Eggleston (21) have presented the hypothesis that the principal function of carboxylase in animal tissue, and also in certain higher plants, molds, and bacteria, is not directly concerned with the oxidation of pyruvate but with the preparatory reaction. The reaction, for which only indirect evidence has been presented, is a carboxylation in which oxaloacetic acid is synthesized from pyruvic acid and carbon dioxide. The oxaloacetic acid so formed is then used in the 4-carbon-dicarboxylic acid cycle of hydrogen-transporting substances known as the "Szent-Gyorgyi cycle." It also forms the basis of the citric acid cycle postulated by Krebs as an integral part of oxidative metabolism. Smyth (22) has presented supporting evidence for such a mode of oxidation of pyruvic acid in the case of *Staphylococcus aureus*. Using vitamin-deficient cells, Smyth found that thiamin could be replaced by the addition of a 4-carbon-dicarboxylic acid. That is, the addition of either thiamin or a compound such as oxaloacetic acid increased the rate of oxidation of pyruvic acid by vitamin-deficient cells of the staphylococcus.

Although Krebs' hypothesis for the mechanism of pyruvic acid oxidation is most attractive, its general occurrence has not been well substantiated as yet. It is to be remembered that this scheme would hardly fit in with the convincingly established fact that the enzyme carboxylase itself causes the quantitative decarboxylation of pyruvic acid. If thiamin is postulated to act principally as an enzyme system for the synthesis of oxaloacetic acid, the importance of the decarboxylation mechanism recedes entirely into the background. It is true that the mechanism for the oxidative degradation of pyruvic acid, pro-

posed by Krebs in connection with the "citric acid cycle," would make a decarboxylation unnecessary. However, there are entirely too many facts supporting the view that decarboxylations, too, are of primary importance in metabolism, to permit the discard of this mechanism.

In view of the significant position pyruvic acid holds as an intermediate product in the metabolic processes in general, experiments were conducted to determine whether the findings of Smyth on the substitution for thiamin of members of the 4-carbon-dicarboxylic acid are applicable in the case of *Prototheca*. The results of experiments in which succinic, fumaric, or malic acids were added in catalytic amounts to suspensions of vitamin-deficient cells oxidizing pyruvic acid do not support Krebs' postulate. In no case did the addition of these acids result in stimulation of the rate of oxygen utilization. The presence of thiamin seems essential to permit the oxidation of pyruvic acid by *Prototheca zopfii*. This observation tends to throw additional doubt on the general validity of the citric acid cycle as the only mechanism for the oxidative decomposition of pyruvic acid.

The results obtained with *Prototheca*, therefore, lead to the conclusion that the function of thiamin as a building block for carboxylase implies the regular occurrence of genuine decarboxylation reactions. Whether these must be considered as straight decarboxylations or as oxidative decarboxylations remains for further investigation. In the event that an oxidative decarboxylation is involved in the metabolism of *Prototheca* the combined function of carboxylase and an additional hydrogen acceptor would, of course, be indicated (see e.g., Long and Peters (23) and Peters (24)). However the main argument put forward here to stress the importance of thiamin (carboxylase) as a decarboxylating agent, remains unaltered. The experimental results definitely indicate that the need of thiamin by *Prototheca* is immediately concerned with the decomposition of  $\alpha$ -keto acids.

#### STUDIES ON THE OXIDATION OF GLYCOLIC ACID BY *PROTOTHECA ZOPFII*

Barker's investigation of the mechanism involved in the synthesis of carbohydrate from simple fatty acids, such as acetic, by *Prototheca* resulted in a deadlock because any scheme that could be postulated for the oxidative degradation of acetate involved acids as intermediate products which the organism was incapable of utilizing as substrates. When the alga was found capable of oxidizing such acids, and conditions could be specified under which a study of their metabolism is possible, an experimental reexamination of conceivable mechanisms for the decomposition of simple fatty acids became feasible.

An investigation of the mechanism involved in the oxidative assimilation of a utilizable substrate must of necessity consider two important phases of the process—the decomposition of the substrate and the synthesis of cell material

The theoretical basis upon which the subsequent experiments were conducted will be developed in the following section

### *Theoretical Considerations*

Although it has long been known that a definite relationship exists between the breakdown and assimilation of foodstuffs, oxidation and synthesis have been considered as more or less separate reactions in which the assimilation reactions, giving rise to products possessing greater free energy than that of the substrate, can acquire energy from the simultaneously occurring dissimilation process in which the free energy decreases. As long as the amount of energy liberated in the catabolic process is in excess of that required by the anabolic reactions, energetically coupled reactions of this type are quite possible on the basis of thermodynamic considerations.

A clearer understanding of the mechanism involved in biochemical processes concerned with the breakdown of foodstuffs has resulted in the possibility of also interpreting assimilatory processes as chemically intelligible step-reactions, not materially different from those operative in catabolism. The general principles of the mechanisms involved in catabolic processes may be briefly summarized. Such a biochemical process can be considered to consist of a chain of individual step-reactions, each step constituting a simple, chemically understandable type of reaction whose common property is the transference of hydrogen from one constituent to another. Each step is a thermodynamically exergonic reaction.<sup>2</sup> This attempt to interpret anabolic and catabolic processes as being closely intermingled chemical reactions does not deny the existence of energetic relations but aims at elucidating the chemical mechanisms for energy transfer which would obviate the necessity of considering the energetic coupling of two sets of chemical reactions which are not known to possess any material link.

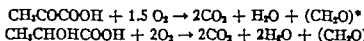
The first broad attempts to formulate a chemical mechanism of energy transfer were those of Kluyver (26, 27) who opened the way for further advances. Although the proposed "mechanisms" may no longer be considered as tenable or probable, the fundamental principle remains a valuable working hypothesis. This embodies the idea that, in the course of the degradation of the substrate, intermediate products arise which can be exergonically converted into the products of assimilation. Thus the structure of the intermediate products is all important in the process of synthesis while the gradual degradation of the initial substrate down to the point of the formation of the essential product plays no *direct* rôle in the assimilation process itself, but is merely the preparation of the essential building block for synthesis. Giesberger (3) developed this idea in his concept of "chip-respiration" in which carbon dioxide and water formed during the oxidative process are regarded as "chips" or waste products of the main reaction. This concept of oxidative assimilation, therefore, places the main emphasis upon the structure of the raw material. Any compound which could be postulated to give rise to an intermediate product possessing the characteristics required to enable it to serve as an initial substrate for exergonic synthetic reactions, would serve the purpose of synthesis to the extent to which it

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<sup>2</sup> The term "exergonic" is used in preference to "exothermic" in accordance with Coryell's proposal (25)

could contribute the necessary intermediates. Although little work has been done on a study of the mechanisms of assimilation there are indications in the literature which lend strong support to the above views

Clifton and Logan (28), investigating the oxidative assimilation of various compounds by *Escherichia coli* found that the oxidation of lactic acid proceeds in a manner similar to that of pyruvic acid. The oxidation of these two compounds can be represented by the following equations



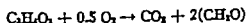
\* $(\text{CH}_2\text{O})$  is here used to represent a compound having the empirical formula of a carbohydrate.

It is a general observation that, in the course of its oxidation, lactate passes through the stage of pyruvate by the loss of two atoms of hydrogen. Therefore, it may be assumed that the same intermediate products would arise in the oxidation of each of these two acids. This is substantiated by the above equations which show that *Escherichia coli* converts one-third of the total carbon of both lactate and pyruvate into primary assimilation products despite the fact that the concomitant oxygen consumption is materially greater with lactate than with pyruvate. This implies that simple energetic considerations fail to account satisfactorily for the situation because more energy becomes available in the oxidation of lactate than in the oxidation of pyruvate. Conversely the formation of carbohydrate storage products from pyruvate would require more energy than from lactate. If, therefore, catabolic and anabolic processes represented merely two types of reactions coupled energetically, then the extent of assimilation should be appreciably greater with lactate than with pyruvate. The very fact that equal portions of both substrates appear in the form of assimilation products thus strongly supports the contention that the nature of special intermediate products is far more important than energetic relationships.

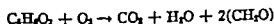
Clifton and Logan also found that the same amount of assimilation occurs during the oxidation of succinic as during the oxidation of fumaric acid although the free energy of succinate is greater than that of fumarate.

The results of Doudoroff's (29) studies on the oxidation of various substances by *Pseudomonas saccharophila* have shown that this organism carries out an oxidative assimilation in much the same manner as that described by Barker (2) Giesberger (3), and Clifton and Logan (28) for other microorganisms. The broader studies of Doudoroff showed that sugars, both hexoses and disaccharides, as well as lactic and pyruvic acids are respired with the complete oxidation of one-third of the substrate and the assimilation of two-thirds. The reaction for each substrate could be represented by a simple stoichiometric relationship, as shown by the following equations

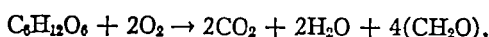
Pyruvic acid



Lactic acid



## Glucose



## Sucrose



From these equations it is apparent that the thermodynamic efficiency with which these substances are assimilated increases in the order carbohydrate, lactate, pyruvate, and that the actual extent of synthesis is directly dependent upon the number of carbon atoms contained in each. Here again, a comparison of the energy released in the oxidation of carbohydrates, pyruvate, and lactate indicates that synthesis is consequently dependent on a chemical mechanism concerned with the intermediate products of metabolism rather than on a purely energetic coupling between separate reactions of oxidation and of synthesis.

By the demonstration that pyruvic acid could be isolated as an intermediate product in the oxidation of glucose, Doudoroff was able to support the indications, presented in the equations for the oxidative assimilation of the sugars, that the metabolism of the mono- and disaccharides would proceed by way of the three-carbon compounds.

*Lactate and Pyruvate Oxidation by Prototheca zopfii*

The above examples clearly show that a comparison of the decomposition of structurally related compounds has, in the case of *Escherichia coli* and *Pseudomonas saccharophila*, supported the idea that a chemical mechanism is operative in processes of oxidative assimilation. Since previous experiments on the oxidative metabolism of *Prototheca zopfii* had not included such structurally related compounds, a comparative study was made of the oxidation of pyruvic and lactic acids by this colorless alga.

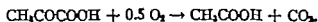
The oxidation of these two acids by *Prototheca* was found to correspond to that for *Escherichia coli* and to differ markedly from that for *Pseudomonas saccharophila*.

During the rapid oxidation of pyruvic acid by *Prototheca*, the ratio of carbon dioxide production to oxygen consumption was found to be between 1.20 and 1.37 with an average of 1.31 for four experiments. The theoretical value required by the equation is 1.33. The R/Q decreased gradually to that found for autorespiration at the time when the acid was completely used up. Data from a number of experiments indicate that autorespiration is completely suppressed during the oxidation of pyruvic acid. The R/Q for lactate oxidation was found to be approximately 1.0, which also agrees with the theoretical.

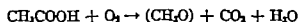
Again, the above experimental results fit in much better with a chemical than with a strictly energetic concept of the mechanism for an assimilatory process. The equations show that the conversion of lactate to pyruvate may well proceed without being accompanied by the formation of reserve materials. It is even possible to postulate further a rational pathway for the subsequent

decomposition of pyruvic acid which is entirely in harmony with the experimental results

The experiments on the influence of thiamin on pyruvic acid decomposition by *Prototheca zopfii* make it logical to accept the occurrence of a decarboxylation mechanism in the oxidation of pyruvic acid. In view of the complete lack of alcohol production by *Prototheca* under anaerobic conditions, the most likely fate of pyruvic acid would appear to be an oxidative decarboxylation. This would result in the production of equimolar amounts of carbon dioxide and acetic acid and would involve the utilization of one-half mol of oxygen per mol of pyruvic acid

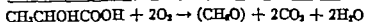
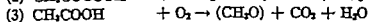
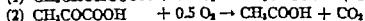
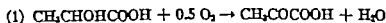


The oxidation of acetic acid has been extensively investigated by Barker, and can be expressed by the equation



The sequence of stages in the oxidation of pyruvic acid could then be represented by a summation of these two equations. This yields a final equation identical with that experimentally determined.

Similarly the consecutive steps for the oxidation of lactic acid could be formulated as follows



Again, the final equation is in complete agreement with the one derived from experimental data. The first two steps are simple reactions for which much evidence had been accumulated in a number of instances and with a variety of organisms. These steps may be considered as elementary ones whose intimate mechanism can be investigated only by special enzyme studies. This is, however, not true for the third state, which not only leaves the question of intermediate products in the acetate oxidation unanswered, but which also 'hides' the mechanism of the assimilation process proper. It is, therefore, apparent that the reasons which prompted the postulation of these series of reactions for the decomposition of pyruvic and lactic acids inevitably led to the desire to study the mechanism of acetate oxidation in more detail.

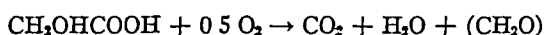
#### *Experiments on the Oxidation of Glycolic Acid by Prototheca zopfii*

Of the two main pathways for the decomposition of acetic acid outlined in the introduction the one involving the successive oxidation to glycolic and glyoxylic acids appears to be the simpler. If the oxidative metabolism of



acetic acid were to proceed through glycolic acid as an intermediate, an investigation of the oxidation of glycolic acid could be expected to show that its decomposition occurs in a manner similar to that described for acetic acid, and an oxidative assimilation as a result of the decomposition of glycolic acid could be expected which would be even more spectacular than that found in the case of acetic acid. The formation of assimilation products from such simple compounds would involve only the methylene group, the  $\text{—COOH}$  group being lost. The former group is more oxidized in the case of glycolic acid than it is in acetic acid and therefore more nearly conforms to the empirical formula of the assimilated material. Therefore, the same proportion of assimilation might occur per mol of glycolic as per mol of acetic acid, while being accompanied by an oxygen consumption of only one-half the magnitude. This situation is similar to that discussed above in the comparison of the oxidation of lactic and pyruvic acids.

On the basis of simple stoichiometric relationships, the equation for glycolic acid might be represented as



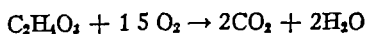
Since the energy obtainable from the oxidation of acetic acid is twice the amount obtainable from glycolic acid, a demonstration that the oxidative assimilation of glycolic acid could be represented by the above equation would effectively rule out the occurrence of coupled catabolic and anabolic reactions in a strictly energetic sense.

The addition of 0.01 mM of glycolic and 0.01 mM of glyoxylic acid to aliquot suspensions of non-proliferating cells of *Prototheca zopfii* resulted in an increase in the rate of oxygen consumption over that of control suspensions. The higher respiratory rates show *Prototheca* to be capable of utilizing the two acids postulated as occurring as intermediates in the Bernhauer scheme for the oxidation of acetic acid.

#### *Quantitative Studies on the Oxidation of Glycolic Acid*

Attempts to establish a balanced equation for the oxidation of glycolic acid by *Prototheca* resulted in the unexpected observation that the amount of oxygen consumed was far in excess of the amount of oxygen that would be required to bring about a complete combustion of this substrate.

The complete oxidation of 0.01 mM of glycolic acid, in agreement with the following equation



requires the uptake of 336 mm<sup>3</sup> of oxygen.

The addition of 0.01 mM of glycolic acid to suspensions of cells having a moderately high rate of autorespiration, resulted in the utilization of 1.89 times

the amount of oxygen needed for complete combustion. If the oxygen consumed is uncorrected for autorepiration, this value is increased to 2.44 times. The addition of 0.01 mM of glycolic acid to suspensions of cells having a lower rate of autorepiration resulted in a value of 1.54 times corrected for autorepiration and 1.85 times if no correction is made.

The addition of different amounts of glycolic acid to several equal portions of cell suspensions showed conclusively that in all cases the oxygen consumption attained values greatly in excess of those required for complete oxidation of the added substrate. Data from nine different experiments, in which suspensions of cells having quite different rates of autorepiration were used, show that the amount of oxygen consumed during the oxidation of equal amounts of glycolic acid varied from 1.34 to 3.57 times the amount of oxygen that would be required for complete oxidation of this substrate. Each of these values is that obtained after correction for autorepiration of control suspensions.

#### *Explanation of the Excess Oxygen Consumption in the Oxidation of Glycolic Acid*

The unexpected oxygen consumption upon the addition of glycolic acid to suspensions of non proliferating cells of *Prototheca* indicates that this acid must exert a catalytic effect on the metabolism of this organism.

To test this hypothesis, aliquot portions of heavy suspensions of washed cells were suspended in phosphate buffer solution at pH 4.0. Each portion was placed in shallow layers in rotating bottles and incubated at 30°C for 12 hours. One portion was given no added substrate but allowed to carry on endogenous respiration only, resulting in the production of 'starved' cells. During the incubation period, small amounts of glycolic acid were added to the second portion at intervals of sufficient duration to insure that meanwhile the previous addition had been completely oxidized.

The autorepiration of the normal "starved" and the glycolic acid treated organisms was measured at the end of the incubation period. The rate of respiration of the organisms which had previously been oxidizing glycolic acid was found to be but 72.2 per cent of the rate of the "starved" cells. This observation indicates that the reserve cell material had been oxidized more rapidly in the presence of glycolic acid than in its absence, and that the residue remaining available for autorepiration was sharply reduced in the experimental organisms.

Addition of 0.001 mM of glycolic acid to 2.0 ml suspensions of both types of cells resulted in a rapid uptake of oxygen. The cells previously treated with glycolic acid consumed a volume of oxygen, over that for autorepiration, equal to 1.75 times the amount needed for complete combustion of the acid added. In contrast, the normally starved cells utilized an amount of oxygen equal to 2.47 times that needed for complete oxidation. This may also be

taken as an indication that the oxidation of glycolic acid by non-growing cells of *Prototheca* causes the oxidation of cell material in addition

In two experiments carried out with cells having a very high rate of autorespiration the addition of 0.001 mM of glycolic acid resulted in the uptake of an amount of oxygen, corrected for autorespiration, equal to 3.57 and 3.22 times the amount necessary for total combustion of the acid. This may be compared with an average of 1.92 for four experiments carried out with cells having a more "normal" rate of autorespiration.

That the oxidation of glycolic acid by *Prototheca* does affect the autorespiration is further evidenced by the results obtained in experiments in which two successive additions of 0.001 mM of glycolic acid were made to suspensions of cells having a high rate of autorespiration. The first addition resulted in the uptake of a quantity of oxygen equal to 3.16 times the amount needed for complete oxidation of the acid. An equal amount of the acid added to the suspension at the time the first portion was completely decomposed caused an uptake of oxygen equal to but 2.08 times that necessary for total oxidation. The addition of 0.002 mM of glycolic acid to the suspensions resulted in the uptake of the same amount of oxygen as when the substrate was added in two equal portions.

To determine whether glycolic acid has an effect on the ability of the cells to carry out an oxidative assimilation, and also to test if glycolic acid could cause an oxidation of newly assimilated cell materials, experiments were carried out in which the oxygen consumption of aliquot suspensions of cells treated in four different ways, was compared. To one sample 0.001 mM of glycolic acid alone was added, another, initially treated in the same way, was supplied with 0.01 mM of acetate after the glycolate had been consumed, both acids, in the above stated amounts, were added simultaneously to the third portion, and in the fourth suspension the glycolate was introduced following the decomposition of an initial supply of 0.01 mM of acetate. The data so obtained are presented in Fig. 6.

The addition of glycolic acid alone to the suspensions of cells used for these experiments caused an oxygen uptake of 1.34 times the amount required for the complete oxidation of the acid. The subsequent addition of acetic acid resulted in the consumption of 1 mol of oxygen per mol of acetate which is identical with the values obtained for the oxidative assimilation of this substrate by "normal" cells. The suspension to which both acids were simultaneously added, showed a total oxygen uptake of the same amount as the total consumed by the suspension to which glycolic acid was added prior to the addition of acetic acid. The results of these two experiments indicate that glycolic acid has no effect on the ability of *Prototheca* to assimilate a typical substrate. In the case in which glycolic acid was added after the suspension had completed its oxidative assimilation of acetic acid alone, the addition of

0.001 mM of glycolic acid resulted in the uptake of 1.64 times the amount of oxygen required for the complete oxidation of the glycolic acid. A comparison of this value with that obtained for the oxidation of glycolic acid by an aliquot portion of cells which had not oxidized acetic acid (1.34) indicates that glycolic acid caused the oxidation of some of the cell material assimilated during the oxidation of acetic acid and may be considered as additional evidence that the

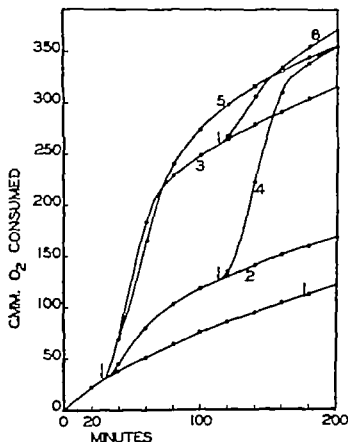


FIG. 6 Influence of glycolic acid on the oxidative assimilation of *Prototheca zopfii* (1) autorespiration (2) 0.001 mM glycolic acid (3) 0.01 mM acetic acid (4) 0.01 mM acetic acid added after decomposition of 0.001 mM glycolic acid (5) glycolic acid and acetic acid added simultaneously (6) 0.001 mM glycolic acid added after decomposition of 0.01 mM acetic acid. Arrows indicate time at which substrates were added.

oxidation of glycolic acid by *Prototheca* has an effect on the autorespiration of these cells.

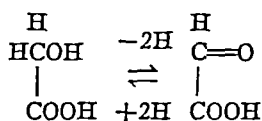
#### *Comparison of the Action of Glycolic Acid with That of Known Biochemical Catalysts*

With the exception of glycolic acid all the substrates so far tested with *Prototheca zopfii* are oxidized in such a manner that a simple stoichiometric relationship exists between the number of substrate molecules disappearing and the number of molecules of oxygen consumed and of carbon dioxide pro-

duced. These relationships permit the formulation of simple, balanced equations, representing the over-all result of the metabolic activity. Also, in all cases, with the exception of glycolic acid oxidation, the quantity of oxygen consumed appears to be a definite fraction of that required for complete oxidation of the substrate.

The unexpectedly high values obtained for oxygen consumption during the oxidation of glycolic acid can be explained only on the basis that this substance functions as a "respiratory catalyst." Thus it becomes attractive to compare the action of glycolic acid with that of substances known to be biochemical catalysts.

Since the general effects of glycolic acid on the oxidative metabolism of *Prototheca zopfii* are so very similar to those which led to the proposal of the Szent-Gyorgyi (30-32) and Krebs cycles (33, 34) the question arises whether it is possible that glycolic acid also might participate in a similar catalytic cycle. The two previously postulated cycles depend largely upon the occurrence of related hydroxy and keto acids. Such relations are readily conceivable for the system glycolic-glyoxylic acids



Therefore, the possibility of a glycolic acid-glyoxylic acid cycle, functioning as a simple type of hydrogen-transporting system, is far from remote.

Against this interpretation is, however, the fact that glyoxylic acid is respired in a "normal" manner by *Prototheca*. This substrate does not appear to possess any catalytic properties such as it would demonstrate if it were a participant in a cyclic reaction.

While this observation makes it, therefore, unlikely that the catalytic effect of glycolic acid on cellular respiration by *Prototheca* is due to its action as a factor of a simple hydrogen-transporting system, a more complicated manner of its participation in metabolism may be considered. The function of glycolic acid in a mechanism similar to that postulated for oxaloacetic acid in the Krebs cycle would imply that glycolic acid is condensed with some oxidizable substance resulting in the synthesis of a compound which is more easily oxidizable than the metabolite itself. The nature of this type of mechanism as applied to glycolic acid is not clear. It is theoretically possible that two mols of glycolic acid could couple to form malic acid in a manner similar to the postulated synthesis of succinic acid from two mols of acetic acid in the Thunberg scheme. However, the addition of malic acid to suspensions of non-proliferating cells of *Prototheca* does not produce a catalytic effect as would be expected if this substance were to arise from glycolic acid "condensation."

The observed action of glycolic acid does suggest an interplay of this substance with some oxidizable cell constituent. However, the nature of the latter is completely unknown and therefore further speculation at this time would seem futile.

It is impossible to evaluate the available quantitative data to determine the relation between glycolic acid used, oxygen consumed, and carbon dioxide produced because it is impossible to separate the gaseous exchange due to the oxidation of glycolate from that arising as a result of the induced oxidation of cell material. For a detailed discussion of the general difficulties encountered in evaluating the portion of metabolism to be ascribed to autorepiration, reference is made to the work of Barker (2), Doudoroff (29), and Thomas (35).

All that can be definitely concluded from the present studies on the oxidation of glycolic acid is that this substance acts in a catalytic capacity and, therefore, the mechanism of acetate oxidation does not go through glycolic acid as an intermediate.

The discovery that *Prototheca* can utilize substituted acids has made possible an investigation of the intermediate stages of acetate oxidation. However, the first approach based on Bernhauer's scheme for acetate degradation, yielded information which makes it necessary to discard this as a likely pathway. With the mechanisms proposed for acetate breakdown thus restricted, studies on other possible intermediates are necessary. Preliminary investigations of one of the condensation reactions of acetate, that of Thunberg, have yielded certain results which indicate this scheme also to be unlikely. By elimination, therefore, the most profitable mechanism for acetate degradation remaining for future investigation is that of a condensation reaction with the formation of acetoacetate and its subsequent oxidation.

#### SUMMARY

The metabolism of *Prototheca zopfii* was investigated in an attempt to establish the specific function of its growth factor, thiamin. A study of the oxidative decomposition of various substrates by this organism demonstrated that the addition of catalytic amounts of thiamin to vitamin-deficient cells causes a pronounced stimulation in the rate of oxygen utilization during the degradation of certain compounds.

The phosphoric ester of thiamin is known to be the prosthetic group of carboxylase. The fact that this enzyme is involved in the decomposition of pyruvic acid suggested that this  $\alpha$ -keto acid might be an important intermediate product in the metabolism of *Prototheca*. Pyruvic acid, however, was not included in the list of organic substances which Barker had reported as utilized by this alga. Barker's observations were confirmed, but subsequent experiments led to serious doubts as to the validity of his interpretation. Further investigations resulted in the establishment of environmental condi-

tions which permit this alga to readily decompose pyruvic acid, as well as nearly all other organic acids tested. This can be accomplished by providing a milieu of sufficiently low pH to insure the presence of undissociated acid molecules.

The stimulatory effect on the rate of oxygen consumption, caused by the addition of minute amounts of thiamin to suspensions of vitamin-deficient cells of *Prototheca* respiring pyruvic acid, indicates that the presence of thiamin results in the synthesis of enzyme systems which are involved in the decomposition of pyruvic acid.

Experimental data on the oxidation of pyruvic acid and other organic compounds are discussed in the light of various hypotheses which have been advanced concerning the rôle of carboxylase in the decomposition of pyruvic acid. The conservative conclusion which can be drawn from the available information is that there appears to be no justification for a belief that thiamin and carboxylase are functional in biochemical reactions other than in decarboxylation and carboxylation processes.

The discovery of the ability of *Prototheca* to utilize substituted and dicarboxylic acids led to further studies on the mechanism of oxidative assimilation. The results of these investigations are in agreement with those of Clifton and Logan, and of Doudoroff, and indicate the existence of a relatively simple chemical mechanism of assimilation rather than of a strictly energetic coupling of catabolic and anabolic reactions.

A consideration of possible mechanisms for the oxidative assimilation of pyruvic and lactic acids indicates acetic acid as the most likely starting point for the assimilatory process proper.

Experimental investigations of the mode of acetate breakdown began with studies on the oxidation of glycolic acid. This substance is shown to be an oxidation catalyst in the metabolism of *Prototheca zopfii*. The exact nature of the catalytic function has not yet been determined.

It is a great satisfaction to be able to thank Dr. C. B. van Niel for suggesting the present study and for the stimulating advice, the sagacious criticism, and the encouragement which he gave so unstintingly during the time it was my privilege to work under his inspiring direction. In addition, I am very much indebted to my associates and to various members of the staff of the Hopkins Marine Station for their numerous courtesies and willing assistance at all times.

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# THE QUANTUM YIELD OF OXYGEN PRODUCTION BY CHLOROPLASTS SUSPENDED IN SOLUTIONS CONTAINING FERRIC OXALATE\*

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## INTRODUCTION

The evolution of oxygen from chloroplasts suspended in solutions containing ferric oxalate was discovered by Hill (1937) and has aroused considerable interest because this reaction appears to be similar in many ways to the oxygen evolution step of normal photosynthesis. It has been investigated further by Hill (1939), Hill and Scarisbrick (1940 *a*, 1940 *b*, 1940 *c*), and by French and Anson (1945), and has been discussed by Johnston and Myers (1943). With the intent of further characterizing the nature of this reaction, we have made some measurements of its quantum yield. If the quantum yield of the Hill reaction was approximately the same as that for oxygen production by normal photosynthesis, it might be taken as an indication that the two processes were similar or possibly identical. The importance of knowing whether the Hill reaction is closely related to the oxygen evolution step of photosynthesis lies in the fact that the Hill reaction takes place in material more amenable to biochemical investigation (i.e. isolated, dried, or disintegrated chloroplasts (French and Anson 1945)).

The quantum yield of photosynthesis in intact *Chlorella* cells has been found to be about 0.09 molecule of oxygen per quantum of light energy by Emerson and Lewis (1943), by Manning, Stauffer, Duggar, and Daniels (1939), and by Rieke (1941). In contrast to this, Gaffron (1927) has reported values of about 1.0 for the quantum yield of photooxidation of organic substrates by chlorophyll in solution. Very small yields of about 0.01 have been postulated for photooxidation processes in live plants by Franck and French (1941).

## EXPERIMENTAL PROCEDURES

*1 Preparation and Treatment of Suspensions*—A large number of the experiments were performed with chloroplast suspensions obtained from market spinach. The healthy young leaves were placed in tap water cooled with ice cubes and were exposed to the illumination from a north window for an hour before use. The leaves were drained free of water and were macerated in a Waring blender which contained

\*Grateful acknowledgement is made for grants from the Graduate School of the University of Minnesota and for apparatus supplied through the courtesy of professors J. Valasek and G. O. Burr of this university.

enough 0.5 M sucrose solution to cover the leaves. The liquid was filtered through a clean handkerchief and the chloroplasts collected by centrifugation as described by French and Anson (1945). All operations were carried out in a refrigerator room at a temperature of about 5°C. The desired volume of chloroplast suspension was added to a solution which contained 0.05 M  $K_2C_2O_4$ , 0.01 M  $FeNH_4(SO_4)$ , 0.02 M  $K_3Fe(CN)_6$ , 0.20 M sucrose, and 0.17 M sodium sorbitol borate.<sup>1</sup>

The solution containing the experimental material was placed in a round, flat-bottom manometric vessel with one side arm. The side arm was filled with 0.5 ml of a 10 per cent NaOH solution which was prevented from "creeping" with a paraffin barrier. To shorten the temperature equilibration time after the chloroplast suspension was added to the reagents, it was customary to first bring the vessel and the reagents to the temperature of the thermostat, and then add the chloroplast suspension to the reagents. When properly equilibrated, neither the reagents alone in dark or light, nor the reagents plus the chloroplast suspension in the dark, showed any pressure change after the manometer stopcocks were closed. Before the addition of the chloroplast suspension to the manometric vessel, chloroplast chlorophyll concentration was measured photometrically as described by French and Anson (1945). Preliminary experiments made with single Warburg manometers showed that long observation periods were necessary because of the small reaction rate. Construction of a differential manometer with a small bore capillary tube increased the sensitivity of the apparatus so that the readings could be made in much less time, with greater accuracy than with single manometers. This was imperative since it was found that at 10°C and in contact with the Hill reagents, the chloroplast suspension lost a small part of its oxygen-producing ability during the first 5 minutes of the experiment. For this reason, in the calculation of the reaction rate, greater emphasis was given to the rate during the initial portion of the illumination period. A second illumination period, separated from the first by either a period of darkness or a period of white light illumination, was accompanied by a further decreased reaction rate. A protocol of the illumination procedure is shown in Fig. 1.

*2 The Differential Manometer*—Since the differential manometer used in this work is slightly different from the original differential manometer described by Barcroft (1908), a brief description will be given here. The differential manometer used by Warburg and Negelein (1922), Emerson and Lewis (1943), and Rieke (1939) is built with the arms of the capillary some distance apart thus requiring a double cathetometer for precise reading of the level of the manometric fluid in either capillary. By construction of a manometer so that both capillaries were vertical and adjacent to each other as shown in Fig. 2, we have been able to measure the level difference directly with a Bausch and Lomb binocular dissecting microscope fitted with an ocular scale divided into 100 parts. Only one eyepiece was used. The microscope was mounted horizontally on a vertical rack and pinion held on an optical bench. The rack and pinion was movable through an angle of about 10° in a vertical bearing, its position at the two extremes being determined by adjustable screw clamps, so that at either setting one of the capillaries is in the center of the ocular scale. It was

<sup>1</sup>Stock sorbitol borate solutions of pH 6.1, 6.5, and 6.8 were used as a buffer as explained in Table III.

customary to place the image of the right capillary at the zero line of the ocular scale by vertical adjustment of the rack and pinion and then to shift the eyepiece to point at the left capillary, the difference in capillary height being read off the scale directly. Each scale division was equal to 0.114 mm. and the readings were reproducible to better than one division. The illumination of the manometer meniscus was accomplished by a pen type flashlight bulb with a built in lens which was mounted on a separate rack and pinion. Readings were made while the manometer was shaking. The total height difference measurable in this way was about 1 cm. For greater

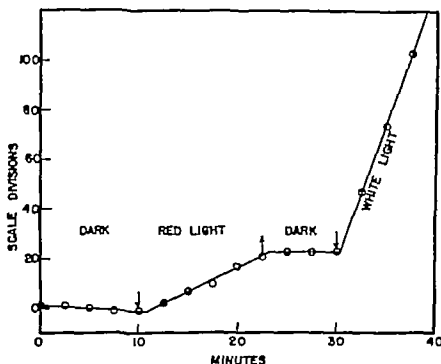


FIG. 1 The net pressure changes are plotted against time for Experiment 5 of Table III. The quantum yield is determined from the difference in slope between the red light period and an average of the two dark periods. The exposure to white light was made to be sure that the chloroplasts were still active after the experiment. The absence of a pressure change due to respiration of the chloroplasts during the dark period is caused by the fact that both the control and the experimental vessels contained similar material. This respiration is very small anyway as compared with the gas exchange due to the Hill reaction.

differences, the stopcock joining the upper part of the two capillaries was opened momentarily to equalize the pressure and to allow the new zero point to be established without opening either vessel to the air. Shaking the manometer and its vessels was accomplished by a rocking motion of 190 excursions per minute through a total path of 0.8 cm. Readings were made at 2.5 minute intervals. The cross-section area of the capillary was  $0.0525 \text{ mm}^2$  somewhat too small for convenience since the viscosity of the fluid can cause a time lag in the equilibrium level with such a small capillary. A manometer fluid with a low vapor pressure, low viscosity, low density, low surface tension, and good wetting properties was found to be xylene containing about 2 per cent each of oleic acid, sorbitol trioleate (Atlas), and "modified" sorbitan trioleate (Atlas). No effort was made to find the precise optimum concentration

of these substances. The specific gravity of the solution used was 0.862 ( $P_0 = 11,980$  mm). It can only be used in an all-glass system. Grease is readily dissolved by this solution.

3 *Light Production and Light Intensity Measurement*—Fig. 3 is a diagram of the equipment used in this study. A 1000 watt T20 tungsten projection bulb with a C13 filament was used as a source and was run at 8.0 amp instead of the rated 8.7 amp in order to prolong its life. A 1 kw voltage-regulating transformer supplied the current. A parabolic mirror with a diameter of 9 inches and a focus of 7 inches concentrated the light into the end of a Pyrex glass tube 2.5 inches in diameter and 3

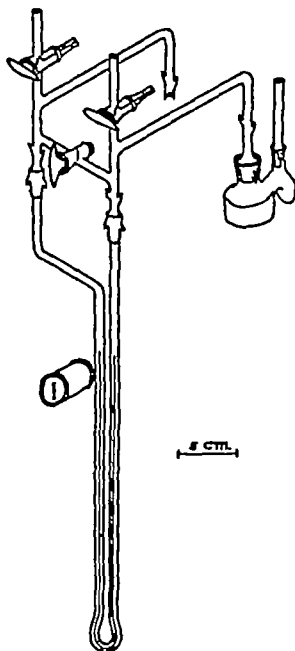


FIG. 2. The differential manometer. A description of its construction and use is found in the text.

meters in length. This tube was filled with distilled water and served to absorb most of the infrared light. After the light emerged from this tube it passed through a Jena RG5 filter and was concentrated on the vessel by means of two condenser lenses and a mirror. A diaphragm with a 1 inch circular hole was placed between the mirror and the manometric vessel. The mirror, diaphragm, and the vessel were placed in a water thermostat at a temperature of about  $10^{\circ}\text{C}$  and constant to  $\pm 0.005^{\circ}\text{C}$  as measured with a Beckmann thermometer. The rate of the reaction was shown to be directly proportional to the intensity of the light used in this work by the introduction of calibrated screens in the beam to reduce the intensity by a known amount. Quantum yields were not increased by this procedure so it was concluded that light was the limiting factor (Experiments 2, 12, 28, and 29 of Table III). Further evidence that the light was not too bright for the attainment of maximum efficiency at least for *Chlorella* photosynthesis is shown in Fig. 4 where a linear rela-

relationship is shown between the total incident energy multiplied by the fraction absorbed and the rate of photosynthesis.

The approximate wavelength distribution of this light beam is given in Table I. This was confirmed by visual observation with a spectroscope. The amount of stray radiation of wavelength longer than  $720\text{ m}\mu$  (about 6.8 per cent) was determined with the thermopile by interposing a Wratten filter No. 88 in the light beam.

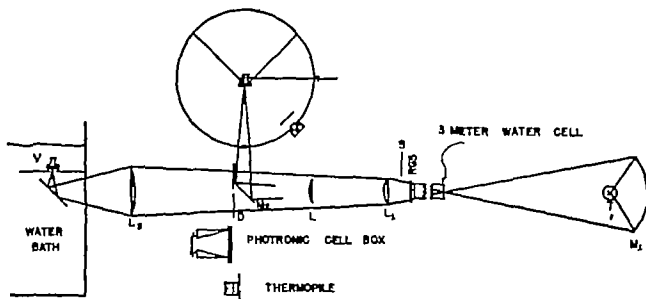


FIG. 3. A diagram of the equipment used for the production and measurement of the light used in this study. The photonic cell box is placed behind the diaphragm *D*, for calibration, and then in the water in place of the vessel *V*, to measure the total light incident on the vessel. The thermopile is later placed so that its sensitive surface is in the plane previously occupied by the diaphragm *D*, to measure the intensity of light used for the photonic cell calibration. *T*, tungsten bulb; *M*<sub>1</sub>, parabolic mirror, focus = 4.5 inches, diameter = 10 inches. *L*<sub>1</sub>, lens, focus = 8 inches, diameter = 4.5 inches. *L*<sub>2</sub>, lens, focus = 7.5 inches, diameter = 4.5 inches. *L*<sub>3</sub> is used only for calibration, in order that the light beam may be concentrated on the diaphragm *D*. This lens and the diaphragm are removed during exposure of the chloroplasts in vessel, *V*, to the light beam. *M*<sub>2</sub>, mirror used only when vessel, *V*, is placed in the sphere for transmission measurements. *L*<sub>3</sub>, lens, focus = 10 inches, diameter = 6.5 inches. *S*, shutter.

For the later experiments the amount of stray radiation was reduced by a further improvement of the light source. A band of light from 660 to 695  $\text{m}\mu$  was isolated from a tungsten lamp with a strip filament which was run at 70 amp and 5 volts. Isolation was accomplished with the aid of a monochromator made of a  $4 \times 6$  inch transmission replica grating and large condenser lenses. The stray infrared light present in this beam was found to be 3.8 per cent. Experiments 13 to 15 and 20 to 24 inclusive (Table III) were made with this improved light source.

The total energy flux of the beam in the position of the vessel was measured with a photonic cell fitted with a metal tube having a ground glass window (protected from the water with a plain glass window) and an internal reflecting cone. Its

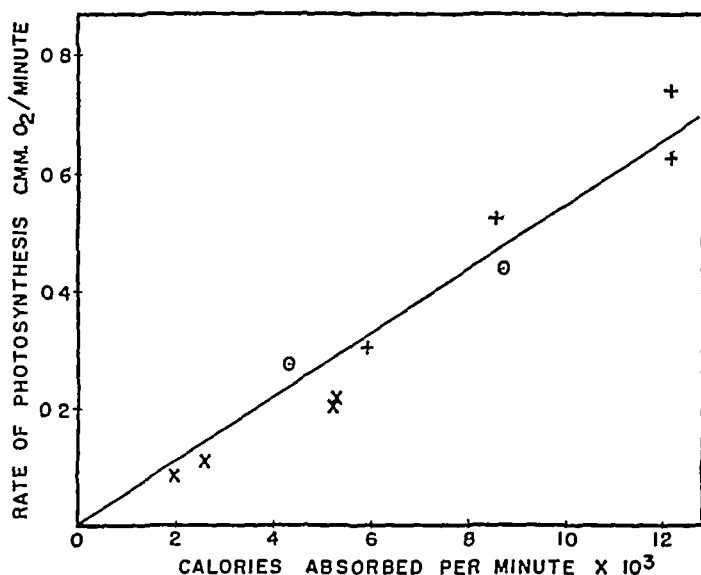


FIG 4 The rate of *Chlorella* photosynthesis is plotted against the energy absorbed. Symbols o, +, and x represent Experiments 27, 28, and 29 respectively in Table III. Calories absorbed = intensity  $\times$  5.09  $\times$  F

TABLE I

*The Wavelength Distribution of Light from a Tungsten Bulb Passing through 3 Meters of Water and a Jena RG5 Filter*

These values were calculated from spectrophotometric measurements of the filter transmission and from the data of Beber based on the International Critical Tables values of tungsten emission and water transmission

Wavelength	Fraction of maximum
<i>mμ</i>	<i>per cent</i>
650	0
660	15
670	41
680	92
685	100
690	95
700	65
710	27
720	11
750	2
800	7
900	0

6.8 per cent  
of the total  
energy

function was to increase the sensitive area of the photonic cell and to enable the cell itself to be kept out in the air while the intensity was measured below the water level. Experiments showed a decrease to about 90 per cent sensitivity near the edge

of the glass, hence only the central portion of the glass surface was used. The photronic cell was connected to a low resistance Type R Leeds and Northrup galvanometer with an Ayrton shunt made of resistance boxes. Each day the photronic cell was calibrated in its integrating box by exposure to the light beam at the same position at which the thermopile was used to measure the energy of the beam. A diaphragm with an opening  $1 \times 3$  cm. was placed in front of the photronic cell in the slightly converging light beam, and the galvanometer deflection noted. The photronic cell was removed and an Eppley surface linear thermopile was mounted so that the junctions were in the same plane in which the diaphragm had been in the photronic cell measurement, and by uniform lateral movement in from 5 to 10 positions the average intensity of the beam was obtained. The thermopile in turn was calibrated daily against U. S. Bureau of Standards lamp C345 (checked also with lamp C149) which afforded an energy measurement in absolute units for the beam of light both outside the thermostat and incident upon the manometric vessel. The current source for the standard lamps was a 6 amp. 115 volt Westinghouse full wave rectifier with a filter circuit which reduced the ripple to about 0.5 per cent under operating conditions. The rectifier was fed from a voltage-regulating transformer. The voltage drop across the lamp was measured with a Weston D. C. voltmeter reputedly accurate to 0.5 per cent full scale. All light measurements and calibrations were carried out as soon as each experiment was completed. Calculated corrections were applied for reflection losses from glass and water surfaces and from the thermopile window whose transmission for the standard lamp radiation was taken as 0.85.

4 *The Measurement of the Fraction of Incident Light Absorbed by the Suspension* — The authors are indebted to Dr. Foster Rieke for instruction in the use of the Ulbricht sphere. Our apparatus differed from that used by Dr. Rieke and will therefore be briefly described here. The integrating sphere consisted of two sheet metal hemispheres 18 inches in diameter. These hemispheres were coated on the inside with a white reflecting surface. The sphere was mounted above the optical bench on which a movable mirror was placed to throw most of the light beam through a lens mounted over a hole in the bottom of the sphere. The light beam came to a focus on the bottom of the manometric vessel which was suspended in the center of the sphere on movable horizontal wire arms (Fig. 3). A photoelectric tube and amplifier system were used to measure the light in the sphere. The phototube was placed in the side of the lower hemisphere and shielded from the light beam by a white baffle plate. In this way only the diffused light was measured. By moving the manometric vessel in and out of the beam, ( $D = 100$ ) measurements of light intensities were made when the vessel was empty when the vessel contained water ( $D_w$ ) when the vessel contained the Hill reagents ( $D_h$ ) when the vessel contained the Hill reagents plus the suspension ( $D$ ), and when the vessel contained India ink ( $D_i$ ). The fraction ( $F$ ) of the incident light absorbed was calculated from the formula

$$F = 1 - \frac{D - D_i}{D_h - D_i}$$

The Ulbricht sphere should give essentially correct values for absorption by pigment alone, corrected for light scattering by particles, if used with monochromatic light. Since the light beam used in this work was not monochromatic, it was neces-



The adults received 1 gram of streptomycin sulfate intramuscularly twice a week, children under 12 years of age received  $\frac{1}{2}$  gram intramuscularly twice a week. Isonicotinic acid hydrazide was administered to all age groups on the basis of 4 mg. per kilo of body weight adjusted to the nearest 50 mg. tablet, and also adjusted as the patient gained in weight. Ten grams of sodium para-aminosalicylate in solution was given daily to adults, and for children the dosage was scaled down according to their weight. No form of collapse therapy was used on this group of patients and they were encouraged to use full lavatory privileges as soon as they were physically able to be up. At the end of three months most of the patients went into the dining room to eat.

Upon admission to the hospital all patients whose sputum was not positive on smear had their gastric contents cultured on three successive days, using modified Lowensteins and Petraghani's media. Gastric contents are cultured monthly until discharge. The original culture is kept for comparison with subsequent cultures to determine whether bacterial resistance to streptomycin or isoniazid is present or if it develops. Roentgenograms of the chest were obtained on admission and at three month intervals. Even old long-standing disease showed some clearing. It is our opinion that the disease remaining after six months represents the destroyed tissue or the scarring resulting from healing. All patients who have not converted their cultures by the end of the third month in the hospital are considered as surgical candidates. Antero-posterior tomographs are taken and bronchoscopy is done.

We recommend surgery when (1) the patient has been positive for three months or more after receiving all three of the antibiotics, (2) when there are extensive localized areas of destruction with or without bronchial stenosis, (3) when the patient is not likely to accept any prolonged period of hospitalization (alcoholics, etc.) and (4) when portions of the lung bound down by adhesions may be salvaged by decortication. If bronchoscopy reveals redness and swelling, then surgery is delayed two to three months and the patient is bronchoscoped again. This bronchitis has constituted a delaying factor for three of our patients. In this series of 22 patients, 25 bronchoscopies have been done.

Twenty thoracotomies with resection have been performed. After surgery, the pathological specimens were cultured using sections of obvious disease, usually from the cavity wall. The following table contains summaries of surgery.

<i>Pulmonary Surgery</i>	<i>Culture Before Surgery</i>	<i>Culture of Specimen</i>
1 Pneumonectomy	Negative	Negative
5 Lobectomies	Negative	Negative
1 Lobectomy	Negative	Positive
1 Lobectomy	Positive	Positive
5 Segmental Resections	Negative	Negative
3 Segmental Resections	Positive	Positive
2 Wedge plus decortication	Negative	Negative

*Extrapulmonary Surgery*

## 5 Genito-urinary tuberculosis

## 3 Nephrectomies.

1 Bilateral resection of the epididymis plus right orchiectomy; patient has moderately advanced pulmonary tuberculosis.

1 Ureteral transplant to the large bowel; 1 kidney functionless, marked involvement of the bladder with stenosis of the ureter where it enters the bladder; also has moderately advanced pulmonary tuberculosis.

## 5 with Bone Involvement

2 Tuberculosis of the knee which have been fused.

1 Tuberculosis of the fibula with a sinus tract that was saucerized and the tract excised; also has moderately advanced pulmonary tuberculosis.

2 Fusions of the spine, one with pulmonary tuberculosis, the other with a sinus tract from lumbar 5 and the sacrum.

Early surgery is possible because shown roentgenologically, maximum clearing had taken place at the end of six months, with most of the change occurring during the first three month period; and, the acute bronchitis had subsided within three or four months from time of admission so that the bronchus would heal when resected. All of these patients have become negative for tubercle bacilli following surgery and there has been no surgical death, no spread or reactivation of disease on the opposite side, and only one bronchopleural fistula which was closed with primary suture and a small thoracoplasty.

*Bacteriological Evaluation:*

General improvement in the condition of our patients is comparable to that described by Pitts, et al, when they used streptomycin and isoniazid, and our conversion of cultures is shown in the following table.

Time in Months	1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.	Over 6 mo.
Number Converting	53	21	8	5	5	2	2
Percentage of Conversions	55.2	21.9	8.3	5.2	5.2	2.1	2.1

One patient was streptomycin resistant at onset of treatment and required five months to convert. Six had isoniazid resistant bacilli at the onset of treatment and for five the period of time before conversion was prolonged; two converted at four months, and three at five months. Both who have been positive over six months have developed organisms that are resistant to isoniazid. Both have been resected and are now negative.

*Toxic Reaction to the Drugs:*

*Streptomycin Toxicity:* Two dermatitis medicamentosa with elevated temperature and eosinophilia occurred on the 28th day of treatment. After the acute reaction subsided, they were given dihydrostreptomycin and the dosage was continued for four and six months until their discharge without any further difficulty. Two with renal tuberculosis developed toxic nephritis with elevation of blood urea nitrogen which returned to normal level within two weeks after stopping streptomycin.

*Para-aminosalicylic Acid Toxicity:* Chills, fever and marked prostration occurred in four who had been receiving the drug from 24 to 49 days and any further attempt to administer it resulted in recurrence of the same symptoms.

*Isoniazid Toxicity:* Only one has had unfavorable reaction to isoniazid. She was a known epileptic who had a recurrence of convulsions but by increasing anti-convulsant drugs it was possible to continue administering isoniazid.

The following table is a summary of the 36 patients still hospitalized and the 60 discharged with regard to extent of disease, average number of months positive, and the amount of therapy that the discharged group received:

Stage	THIRTY-SIX PATIENTS REMAINING IN HOSPITAL		SIXTY DISCHARGED PATIENTS		
	No. of Patients	Average Rate of Conversion	No. of Patients	Average No. Hospital Days	Average No. Months Positive
Minimal	2	1 month	2	243.5	1.67
Moderately Advanced	10	1.7 months	27	200.2	1.67
Far Advanced	17	2.88 months	20	248.3	2.7
Primary	5		4	172.1	
Extrapulmonary (Three with Pulmonary)	5		10	152.3	
Final Averages				207	2.05

DRUGS RECEIVED	Average No. Days Received	Per cent of Time in Hospital
Streptomycin	194.2	95
P.A.S.	160.9	77
Isoniazids	185.3	90

The periods of time required to convert patients admitted with minimal, moderately advanced and far advanced tuberculosis are surprisingly similar, both in the discharged group of 60 and the 36 remaining in the hospital. The length of their hospital stay is generally about the same regardless of the extent of their disease.

### Discussion

When we compare our results using streptomycin, para-aminosalicylic acid and isoniazid with the results of Pitts, et al, using streptomycin and isoniazid, there is little difference between the two programs during the first four months of therapy. Beyond that time, however, the combination of all three drugs seems to be of greater therapeutic value with a higher conversion rate and the emergence of fewer resistant strains of organisms.

The question is raised: Why do not all patients convert their gastric cultures by the end of three months? Bacterial resistance or the development of bacterial resistance accounts for eight of the 14 who did not

convert during the first three months. Three had acute bronchitis and became negative when the bronchitis subsided. Two had poor blood supply to the tuberculous area due to silicosis. The last of the 14, had marked continuous blood loss due to a fibroid uterus and she became negative following hysterectomy when it was possible to maintain her hemoglobin at normal level.

We have not seen intermittantly positive patients. Once they became negative, they remained so even though they were permitted additional activity in the hospital.

There has been great disagreement between the bacteriologist and the clinician regarding the negative cultures found on pathological specimens.<sup>4,5</sup> Since the results of culture from our pathological specimens have been similar to the reports of other authors, and since physical exertion has always been considered the cause of reactivation, we have been returning our patients to their previous occupations and activity immediately upon discharge from the hospital. Many have gone back to hard physical labor, doing farm work, foundry work and carpentry. We examine these every three months and some of this group have been out of the hospital for six months or more. All of these patients have maintained their discharge weights and have no symptoms. There has been no evidence of roentgenological change. These patients have had no chemotherapy since leaving the hospital. We do not know how long the three drug combination should be given, but our patients have received an average of 194 days of streptomycin, 161 days of para-aminosalicylic acid and 185 days of isoniazid out of an average of 207 days in the hospital. If after one year there are no readmissions it would seem that this dosage is adequate.

### SUMMARY

1) When we compare the streptomycin-isoniazid combination with our usage of streptomycin, para-aminosalicylic acid and isoniazid, the three drugs used concurrently and continuously have a greater therapeutic value with a higher conversion rate and the emergence of fewer resistant strains of organisms.

2) It is possible to maintain this regimen of therapy on a high percentage of patients because of the few toxic reactions. The cost is negligible.

3) Surgery after four to six months of this three drug regimen is not only safe but it is desirable because it prevents the development of resistant organisms.

4) Sixty patients have been discharged and returned to their previous occupations, regardless of the amount of activity these occupations require. They have shown no roentgenological change, have maintained their discharge weights or gained, and some have already had negative gastric cultures as out-patients.

### RESUMEN

1) Cuando comparamos la combinación de estreptomicina-isoniacida con el uso de estreptomicina-PAS-isoniacida, se observa que el uso de las tres

drogas simultáneamente tiene un valor terapéutico mayor con una proporción más elevada de conversiones de esputos y menor emergencia de cepas resistentes.

2) Es posible mantener este régimen de tratamiento en un elevado porcentaje de enfermos a causa de las pocas reacciones tóxicas a que da lugar. El costo no es de consideración.

3) La cirugía después de cuatro a seis meses de este régimen de tres drogas, no sólo es segura, sino que es deseable porque previene el desarrollo de gérmenes resistentes.

4) Se han dado de alta sesenta enfermos que han regresado a sus ocupaciones previas sin tener en cuenta el grado de actividad que tales ocupaciones requieren. No han mostrado cambios radiológicos, han mantenido su peso al salir o han aumentado y algunos, han llegado a tener cultivos gástricos negativos en pacientes externos.

### RESUME

1) En comparant l'utilisation d'une part de la streptomycine associée à l'isoniazide et d'autre part de la streptomycine associée au P.A.S. et à l'isoniazide, les auteurs constatent que ces trois produits, administrés simultanément et d'une façon continue, ont une plus grande valeur thérapeutique, négativement plus vite l'expectoration, et provoquent une plus faible résistance des germes.

2) La discrétion des réactions toxiques permet de poursuivre longtemps ce mode de traitement pour une proportion élevée de malades. Le prix de revient en est négligeable.

3) Après quatre à six mois de ce traitement médicamenteux, l'intervention chirurgicale a non seulement perdu ses risques mais en outre elle souhaitable pour éviter le développement de bacilles résistants.

4) Soixante malades ont été autorisés à quitter l'hôpital et à retourner à leurs occupations antérieures, quel que soit le degré d'activité qu'elles exigeaient. Il n'a été constaté chez eux aucune évolution radiologique, ils se sont maintenus au poids qu'ils avaient à leur sortie ou l'ont augmenté, et certains d'entre eux suivis à la consultation ont jusqu'à présent des cultures de tubages gastriques négatives.

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# The Clinical Use of Intravenous Sodium Para-Aminosalicylate and Polyvinyl Pyrrolidone\*

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## Introduction

In a previous report<sup>8</sup> the authors confirmed the work of French investigators<sup>2,3,6</sup> showing that a combination of 25 per cent Sodium Para-aminosalicylate (PAS) in 3.5 per cent aqueous polyvinyl pyrrolidone (PVP) given by intravenous syringe injection results in blood PAS levels which are approximately twice as high and last twice as long in a therapeutic range as does similar injection of 25 per cent PAS without PVP. It was also demonstrated that PVP does not interfere with the antibacterial property of PAS *in vitro* and it does not prevent PAS from passing into the cerebrospinal fluid in adequate amounts. PAS-PVP solution was used therapeutically in a small series of patients for short periods of time without significant toxicity. Therefore it is feasible to use such a preparation in the treatment of tuberculosis and it has an advantage over the usual forms of parenteral PAS in that it may be given in small amounts by syringe injection twice a day.

The purpose of this report is to present further observations on the use of intravenous PAS-PVP in a larger series of patients, including postmortem findings in four. It will also be shown that PAS-PVP has no particular value when given by mouth from the standpoint of the blood PAS levels achieved.

## Method

PAS-PVP is provided as a sterile light amber aqueous solution in 10 cc. ampules containing 25 per cent Sodium PAS and 3.5 per cent PVP. For control studies, a sterile aqueous solution of 25 per cent Sodium PAS was used. PAS-PVP was injected intravenously by syringe in 10 cc. amounts twice a day for the purpose of therapy. The injection was made slowly over a period of five minutes. Proportionately smaller amounts were used in children on the basis of body weight.

Blood level curves were determined after the ingestion of 10 cc. of drug solution diluted to 60 cc. with water and followed by 60 cc. of orange juice. Three patients were given PAS-PVP and three were given PAS alone. Specimens of blood were drawn one, three, six and nine hours after administration of the drug and were stored in the refrigerator over night. The following day the PAS levels were determined by the method of Klyne and Newhouse.<sup>5</sup> The resulting curves were compared with the curves ob-

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tained after intravenous injections of the same materials in six patients who were used as their own controls.<sup>8</sup>

### *Results of Blood Level Determinations*

Figure 1 shows that PAS-PVP when given intravenously (A) resulted in much higher and more prolonged PAS blood levels (average values) than does PAS alone given intravenously (B). This figure further shows that the oral administration of PAS-PVP resulted in blood levels (D) which were not significantly different from those obtained after the use of an equivalent amount of oral PAS alone (C) and both of these curves differ only slightly from the curve obtained after intravenous injection of PAS alone. Since PVP is a polymer which is not absorbed from the gastro-intestinal tract, these findings are understandable. It is apparent that PAS-PVP results in elevated and prolonged PAS blood concentrations only when this combination is administered intravenously.

### *Toxicity of Intravenous PAS-PVP*

Table I summarizes the data on toxic reactions in 39 patients treated with intravenous PAS-PVP for periods varying up to four weeks. Twenty-three received treatment for less than one week. Ten died of their disease. It was necessary to discontinue medication in one case because of pain in the region of the biceps muscle above the site of injection during administration of the drug. Other toxic manifestations were insignificant, including transient slight dizziness in a few patients. Treatment was stopped in the rest of these 23 cases when parenteral PAS was no longer necessary.

Ten were treated for one to two weeks and one died of his disease. Therapy was discontinued in one because of thrombophlebitis. Treatment was stopped in the remainder when intravenous PAS was no longer indicated.

Six were treated for two to four weeks and one died of his disease. Thrombophlebitis necessitated discontinuation of therapy in two cases and

TABLE I: TOXICITY OF INTRAVENOUS PAS-PVP IN 39 PATIENTS  
CORRELATED WITH DURATION OF THERAPY

Duration of Therapy	No. of Patients Treated	Manifestation	TOXICITY	No. of Patients
Less than 1 week	23	Pain in biceps*		1
		Transient lightheadedness		1
		Phlebothrombosis		1
		Transient nausea and warmth		1
1 to 2 weeks	10	Thrombophlebitis*		1
		Phlebothrombosis		1
2 to 4 weeks	6	Thrombophlebitis*		2
		Phlebothrombosis		1

\* Necessitated discontinuation of therapy.

injections were stopped in the other three patients when intravenous PAS was no longer needed.

The indications for intravenous PAS-PVP were as follows: critical forms of tuberculosis such as miliary and meningeal disease, inability to take adequate amounts of PAS by mouth, and major chest surgery for tuberculosis. Those who fell into the latter category were routinely given intravenous PAS-PVP twice a day for one or two days prior to the operation and three or four days after the operation. Because of the possibility that PAS might interfere with the clotting mechanism by lowering the prothrombin level, nine were treated and followed with frequent blood prothrombin determinations; no significant changes were noted.<sup>4</sup>

Four who died were autopsied. They had received two to seven days of treatment before death. No significant histologic change that could be attributed to PVP was found in the various organs. The renal tissue was examined by means of routine H & E, fibrin, mucopolysaccharide and trichrome stains. Excessive granularity was noted in the tubular epithelium by Dr. William E. Ehrlich. This was most pronounced in a patient who died of lymphocytic choriomeningitis (diagnosed as tuberculous men-

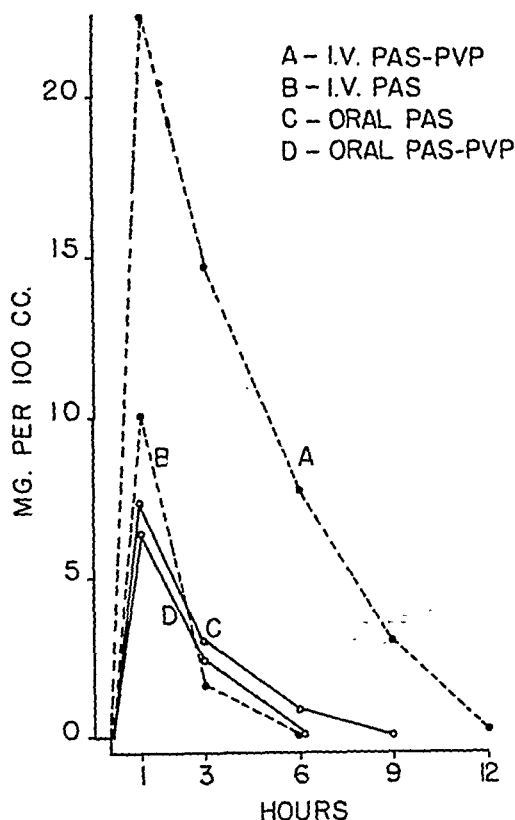


FIGURE 1: Average blood PAS levels after oral and intravenous administration of 2.5 grams of Sodium PAS with PVP and without PVP.



ingitis during life) and constituted what Dr. Ehrich called a "protein storage nephrosis". Whether this was due to the choriomeningitis or to the PVP is difficult to say at this time.

### *Discussion*

Both PAS and PVP<sup>1</sup> have been given intravenously to humans in large amounts without significant toxicity. It is therefore reasonable to assume that the small amounts used in the PAS-PVP solution with the present regimen of therapy for short periods of time are not harmful. The only significant reaction encountered has been local thrombophlebitis in a small percentage of patients after more than one week of treatment. This reaction is undoubtedly due to the high concentration of PAS employed. Since it is uncommon, such reaction does not constitute a deterrent to the use of intravenous PAS-PVP.

PVP is a macromolecular polymer and only 40 to 60 per cent is excreted in the urine during the first few days after infusion. Since no other routes of excretion have been demonstrated, there has been some concern over the ultimate fate of this substance and the possible toxic effects of long term retention. Ravin, Seligman and Fine<sup>7</sup> have studied the excretion, distribution and metabolism of PVP by means of radioactive tracer technics. There is no apparent metabolic degradation of PVP and, since the sole route of excretion is through the kidney, what PVP is not present in the blood is present in the tissues. The highest concentration of PVP is in the organs of the reticulo-endothelial system and retention is longest here. PVP may be excreted in the urine from tissue depots for as long as a year after intravenous infusion. There is, however, no evidence at present that long term retention of PVP is deleterious. Hence it would seem to be safe to use this substance in small amounts for short periods of time in combination with PAS for the treatment of tuberculosis whenever it is advantageous to achieve high blood PAS levels with a minimum of inconvenience and when oral administration of PAS is not feasible. Further discussion of this interesting combination of drugs is contained in our previous report.<sup>8</sup>

### SUMMARY AND CONCLUSIONS

A combination of 25 per cent Sodium PAS in aqueous 3.5 per cent PVP solution has been administered intravenously twice a day to 39 patients for various periods of time up to four weeks. The only significant toxic reaction was thrombophlebitis which occurred in three. Postmortem histologic studies in four cases revealed no lesion that could be definitely attributed to PVP. No change in plasma prothrombin level occurred during therapy.

The advantage of this combination lies in the fact that higher and more prolonged blood PAS levels are achieved than can be obtained with equivalent amounts of PAS alone when given intravenously or by mouth. It has been shown that PAS-PVP given by mouth does not result in blood PAS levels which are significantly different from those which result when equivalent amounts of PAS alone are given orally.

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### RESUMEN Y CONCLUSIONES

Una combinación de solución acuosa de PAS sódico al 25 por ciento con una solución de PVP se administró intravenosamente dos veces al día a 39 enfermos por varios períodos de tiempo hasta cuatro semanas. La única reacción tóxica fué la tromboflebitis que ocurrió en tres. Los estudios post-mortem, histológicos en cuatro casos no revelaron lesiones atribuibles al PVP. No ocurrió cambio en el nivel de protrombina en el plasma durante el tratamiento.

La ventaja de esta combinación radica en el hecho de que se obtienen niveles de PAS más altos y más prolongados que lo obtenido con el PAS sólo cuando se dió por la boca o intravenoso. Se ha demostrado que el PAS-PVP por vía oral no produce niveles de significación diferentes de los que produce el PAS oral solo.

### RESUME

L'auteur à administré, par voie intra-veineuse, deux fois par jour, à 39 malades, pendant un temps variable allant jusqu'à quatre semaines, une solution de 25% de P.A.S. sodique dans une solution aqueuse à 3.5% de polyvinyl pyrrolidone. La seule complication de ce traitement fut une thrombophlébite chez trois malades. Dans quatre cas, il fut amené à faire une étude histologique post-mortem, et celle-ci montra aucune lésion qui puisse être sans discussion attribuée au polyvinyl pyrrolidone. Au cours du traitement, il n'y eut aucune altération dans le taux de la prothrombine plasmatique.

L'avantage de cette association thérapeutique réside dans le fait que l'on peut ainsi obtenir des taux sanguins de P.A.S. plus élevés et plus prolongés que ceux que l'on obtient avec des doses égales de P.A.S. lorsqu'il est administré isolément soit par voie intra-veineuse, soit par voie buccale. Il à été démontré que cette association P.A.S.-polyvinyl pyrrolidone, lorsqu'elle est absorbée par la bouche, n'entraîne pas d'élévation du taux de P.A.S. sanguin nettement différent de ceux que l'on obtient par l'ingestion buccale de P.A.S. pris isolément.

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# The Post-War Tuberculosis Program in the Philippines

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## *Introduction*

The problems faced by the Philippine Commonwealth government at the end of the Second World War included not only those resulting from actual hostilities, but many problems arising from the failure of the Public Health program before the war broke out. In 1941 this program had deteriorated badly and equipment was already obsolete. As a consequence, the danger of large-scale epidemics was great by 1945. The United States came to the assistance of the battered country shortly after the war ended; a budget of \$5,000,000 was appropriated for public health rehabilitation. Of this sum, \$1,000,000 was specifically set aside for tuberculosis control, since this had long been one of the chief public health problems in the Philippines. The fund was to be administered by the Department of Health of the Philippine Commonwealth and the United States Public Health Service; the Philippine government obligated itself to carry on the program alone at the end of five years.

The tuberculosis control program was worked out by Dr. Leroy K. Young, of the United States Public Health Service, and representatives of various local organizations interested in tuberculosis control. The writer was present representing the director of the Bureau of Health. It was realized by all concerned that the sum allotted was small, in terms of the size of the population (about 20,000,000) of the Philippines, and the seriousness of the tuberculosis hazard. Various approaches were considered, but it was finally decided to adopt Dr. Young's suggestion, and concentrate upon the control program which was proving so successful in the United States at that time—mass chest radiography.

## *Results of Large-Scale Chest X-ray Survey*

In a period of five years, about 1,000,000 people were x-rayed by mobile units or at permanent chest examination stations. Approximately 9 per cent of those examined were found to be suffering from tuberculosis of the lungs. If this rate persists throughout the entire population, it would mean that about 1,800,000 people in the Philippines have active and contagious tuberculosis. Fortunately, there is reason to believe that this rate is not typical of the whole population, but there was confirmation of what was already known, that tuberculosis is a major Philippine health problem.

The survey was otherwise of little consequence, even among those who received x-ray films. For the most part, the active cases of tuberculosis were confirmed and then released. There were no facilities for isolation; we had neither the sanatorium beds nor personnel. The great majority of

these known tuberculous individuals remain untreated, uncared for, unisolated, and free to continue spreading infection. It has even proved impossible to provide medicine and supplementary food for these known cases of clinical disease. This episode became another example of how excellent public health programs can become ineffective and wasteful when they are designed without regard for local conditions.

#### *Further Public Health Measures—BCG*

Since we were unable to deal with the cases of tuberculosis that we had, it was obviously foolish to continue to concentrate our program on further case finding, and we were forced to reconsider our approach. The same problem, grossly insufficient funds, remained. At this juncture, BCG was suggested and favorably received. It was felt that since the facilities for isolation, treatment, and education were lacking, immunization was the one remaining approach, offering substantial possibilities. Financial and technical assistance on such a program might be available, it was felt, since the World Health Organization was interested in BCG.

The World Health Organization encouraged this program, and soon after the Philippines became a member, it made available the personnel necessary to begin the undertaking. Dr. Gumersindo Sayago, of Cordoba, Argentina, was among the first workers to arrive; he spent six weeks visiting local chest centers, holding conferences with medical groups, and conducting a two week training course for Philippine medical personnel.

Even before the war BCG had been used in the Philippines, but only on a small scale. Those interested in this early program, including myself, were not particularly impressed with the vaccine at the time, and were inclined to oppose the large-scale program. However, in some degree because of the influence of the World Health Organization, the Philippine government and powerful social groups became enthusiastic. The findings of the early Philippine experiments were neglected in favor of the apparently encouraging reports from South America and Europe. BCG became the official tuberculosis control program of the government and absorbed a great share of the financial resources available. Attempts to reexamine the question have been promptly and firmly discouraged; the writer's protests against the enthusiasm BCG has generated have been bitterly attacked both by officials concerned with the program and by local health leaders.

#### *BCG in the Philippines—Its Feasibility*

The writer's interest in BCG is not new; it began about 25 years ago at the Sixth International Conference on Tuberculosis, held in Rome in 1928. Following that conference, and a tour of the leading tuberculosis centers of Europe, the writer summarized his objections to BCG as follows:

"What should be the attitude of Philippine workers toward this vaccine? The controversy which BCG has occasioned would not be so serious if the question raised by its opponents concerned merely the *effectiveness* of the vaccine. But can we really consider the use of this control measure when

acknowledged authorities seriously question its *safety*? Are we justified in subjecting—to borrow the word of von Pirquet—the next generation to the uncertainties surrounding such a vaccination? . . . We must not allow ourselves to be overcome by a well-meaning desire to be pioneers in this new treatment, this biological novelty that promises nothing short of the elimination of the white plague from the whole world.”

The writer has been interested in BCG since that time. Literature on the subject has been followed sympathetically; prejudice against a control measure is impossible, if it works. Tuberculosis is our leading health problem in the Philippines and the “number one” killer of our people. If the vaccine could be demonstrated to be as effective as its proponents have claimed, its service in these islands would be incalculable.

However, the status of BCG has not materially improved since 1928. The basic questions raised at the Sixth International Conference are still the basic questions; they have not been answered. In all the publications on the subject since that date there is little that touches upon the fundamental immunizing principle of BCG. There is a tremendous amount of information upon its stability, standardization, optimum dosage, dried versus fresh vaccine, methods and routes of injection, and tuberculin criteria and conversion. The writer searched in vain, however, for new views and fresh research on the great question—the nature of its supposed immunizing properties.

Doubts on this matter can be reduced to six main heads:

- (a) What is the nature of the immunological process that is provoked by the entrance of BCG into the human body?
- (b) How does BCG respond in standard tests of immunology?
- (c) Why is not BCG effective against bovine tuberculosis?
- (d) Has BCG even been conclusively proved to be what it is alleged, a strain of attenuated bovine-type bacilli?
- (e) Why should it be a hazard in the presence of pre-existing allergy?
- (f) What has been clinically established of the effectiveness of BCG?

(a) *The Nature of the Immunological Processes that are Provoked by the Entrance of BCG into the Human Body.* Immunity to a particular disease results from the acquired ability of body tissues to destroy invading germs by intracellular digestion (phagocytosis of Metschnikoff) or by extracellular digestion (phagolysis of Pfeifer). It is a fundamental principle of preventive medicine that such immunization is always specific. Why should tuberculosis be the exception to this principle; why should we inoculate for human tuberculosis with bovine bacilli?

(b) *BCG in the Light of Other Immunological Tests.* It is sufficiently established that the blood serum of animals immunized to a given bacterium develops biological products not found in the serum of non-vaccinated animals. One of these elements is *specific precipitins* (Kraus); when the blood serum of an animal immunized against a given bacterium is mixed with a culture filtrate of emulsion of that same organism, a “precipitate” or protein deposit results. *Specific agglutinins* (Gruber and

Durham) show a similar reaction with the difference that an agglutinate rather than a precipitate is formed. In both instances the reaction is specific; cholera serum precipitates only cholera filtrate, and so on.

The question is: "Have the Calmette-Guerin bacilli and the blood of those vaccinated with it been studied for these reactions?" The answer is silence. The vast literature and the large number of experiments done on BCG pass the question by—significantly, we think.

(c) *The Effectiveness of BCG in Bovine Tuberculosis.* The seriousness of the failure of BCG to meet standard immunological tests is magnified by its peculiar failure to confer immunity where such immunity would most reasonably be anticipated—in the treatment of cattle. Again, literature is apt to be non-contributory so far as concrete evidence is concerned. The most prominent fact is that in the countries, such as the United States, where bovine tuberculosis is under firm control, this has been accomplished *without* vaccination. BCG was given extensive trial but did not seem to be efficacious among cattle. The Joint FAO WHO Panel on Brucellosis on the subject of bovine tuberculosis concluded the following:

"Vaccination of livestock, particularly with BCG, may be considered a temporary expedient, applicable under certain conditions of economic hardship when it is necessary to reduce the spread of the disease before eliminating the infected animals. Vaccination has its disadvantages: it may create an allergy non-distinguishable from natural infection; intravenous injection of BCG—which sometimes replaces subcutaneous injection—may produce local or general reactions. Vaccination must therefore be used with caution."

The plain fact is that in no instance has bovine tuberculosis been controlled by the use of BCG. Surely this compound cannot be taken seriously among scientists until some explanation is advanced to explain this unique finding, that a vaccine is more effective against a related but distinct organism than it is against its own parent strain.

(d) *Is BCG Conclusively Proved to be a Strain of Bovine-Type Bacillus Rendered "Non-Pathogenic"?* In contemplating the scientifically incomprehensible findings that have been advanced for BCG, we have occasionally been assailed by a grave misgiving. Are the organisms in this vaccine really attenuated bovine bacilli at all? Or are they only saprophytes, such as Moeller's Timothy Bacillus? We have been assured that this doubt is fantastic, but if so, this can readily be demonstrated. The "personality" of BCG can easily be established by repeating the experiments of Calmette and Guérin and duplicating their results. In the many years that BCG has been studied, this simple procedure has never been done; all of our BCG serum is derived from the original experiments.

(e) *The Positive Untoward Effect of BCG when Injected into Persons with Naturally-Established Tuberculin Allergy.* By all immunologic criteria, a person who is tuberculin-allergic should be one who has a pre-existing tuberculosis infection and thereby already possesses the blood elements which confer specific resistance to subsequent infection. Physicians are constantly cautioned that BCG should not be administered to such persons.

Why? If BCG consists of non-pathogenic bovine tubercle bacilli, as is claimed, there is no conceivable immunologic theory that could account for untoward effects in this instance. Obviously, untoward effects are to be feared. The only situation in which such effects might be feared is if human tuberculosis were so different from bovine that it could not immunize against the latter, but provided instead a fertile situation for bovine pathogens of a low grade of virulence. It would require, in other words, the assumption that some degree of virulence was present in BCG.

(f) *The Positive Role of BCG in Reducing Clinical Infection.* The proponents of BCG do not spend much time in a defense of the theory underlying the preparation; in this instance, scientific understanding and control are of less interest than clinical evaluation. But even here unscientific methods make published results of dubious value.

The most enthusiastic reports on BCG came from South America. I think most students would admit, however, that the failure to provide adequate control groups makes these experiments of little value as evidence for BCG.

Most weight is given to the widespread use of the vaccine in the Scandinavian countries, France and Japan. In any of these situations, it is foolish to credit BCG with all progress, without evaluating other factors. In Sweden, for instance, the part played by an increased standard of living and education on the falling morbidity rate is perhaps impalpable, but it is certainly large. In France the situation is similar. Anderson, in a paper presented to the National Tuberculosis Association in 1950, commented on BCG in that country as follows:

"In view of the attitude toward BCG, which has been maintained in this country for so many years, it appears that we have something of an obligation to answer our own question and to prove, before it is too late, just what this vaccine could do in our population. We have before us, the example of France, where BCG vaccination was begun nearly thirty years ago, where compulsory legislation was enacted last year, and yet where no reliable data could now be obtained, as to what part BCG has played in the history of tuberculosis in the country as a whole. We cannot give unqualified credence to the assertion, that a general marked decline in tuberculosis morbidity and mortality in France and Denmark or any other country where BCG has been used, constitutes evidence that BCG was effective."

In Japan a campaign of inoculation has been undertaken with the most exaggerated claims advanced as to its effectiveness. Of the conviction advanced there by individuals on the SCAP staff and local public health leaders, that BCG could arrest the increasing incidence of tuberculosis and prevent the appearance of all but a few new clinical cases, Myers wrote, "Such a result has never been approached anywhere by the use of a vaccine." According to Dr. Akira Saita, in a statement made in September, 1951, "Tuberculosis is the major disease in Japan today, and is causing the greatest number of fatalities." He added that deaths due to tuberculosis were about 150,000 yearly, with 10 times that number of active cases.

It is somewhat surprising to find proponents of BCG using the World

Health Organization's vaccination of 50,000,000 children as evidence for BCG's further use. The effect of this mass inoculation has not, and cannot be, evaluated. As evidence for or against BCG, it can be anticipated with confidence that this program will always be meaningless. The diverse training of technicians, the lack of standards for interpretation, most especially the lack of a system of controls, guarantees that the results of this gigantic undertaking will always remain an enigma.

It is our conviction that in none of these instances has the effectiveness of BCG been put beyond dispute. Most of the large-scale applications have been debated for 10 years, and authorities on tuberculosis remain unconvinced. No other tuberculosis control measure has been so questionable after such a long period of use. The opponents of this measure are being asked, for the time being, to stop being men of science; to accept this vaccine without the rigorous demonstrations of its harmlessness and effectiveness that are demanded of other medical preparations.

### *Conclusions*

The writer is quite aware of the fact that this article will be interpreted as another hypercritical attack on BCG. However, personal considerations should not be allowed to influence judgment upon so important a matter. It is our dispassionate conviction that BCG has not proved itself elsewhere, and there is no reason to anticipate that it will have any greater effect in the Philippines than it has had in Japan. It is particularly unfortunate that this remedy should appear hard on the heels of our disappointment with mass surveys. BCG represents a continuation of our effort to deal with tuberculosis without taking into account the local conditions in which the disease is generated.

All students would agree, of course, that the factors which contribute to our high morbidity and mortality rates can be adequately summarized in one word: poverty. On the one hand, there is ignorance of the most elementary sanitary methods, malnutrition and overcrowding; on the other hand, lack of facilities for isolation and treatment of known cases of disease, lack of trained personnel, and even lack of finances for medication.

In this situation, it requires no very great amount of imagination to devise a health program that could be guaranteed, over a period of time, to accomplish our ends. It would involve the following:

- (a) Nation-wide education in sanitation and domestic science.
- (b) A program of hospital construction simultaneous with case-finding work.
- (c) A vigorous government program directed to improvement in the standard of living, including provision for housing and social security measures designed to eliminate malnutrition.

All leaders in public health would agree that these measures are the fundamental ones to tuberculosis control; perhaps all would agree that tuberculosis will remain with us as a serious public health problem, BCG or no, until these measures are undertaken. There is, nevertheless, no concerted drive at the present time for such a program.



The fact is that public health officers are trying to be doctors and legislators at the same time. As men of medicine it would seem that their one duty is to diagnose the problem and prescribe the best treatment; it is up to the Philippine Commonwealth to meet the prescription as best as it is able. The medical profession should be inflexible in its diagnosis; it does not dare encourage the laymen responsible for implementing its program with false confidence in less than the most desirable way of meeting the problem. If money *must* be had for an adequate public health program, a lot more will be available than first appeared possible.

Instead, our medical officers are being "realistic". Their attitude is well summarized by the following:

"As a public health man, I consider tuberculosis in this country a major epidemic, which requires immediate and drastic measures. The tested methods of hospitalization and treatment are beyond our means. Education, another tested weapon, is too slow. . . . It seems reasonable, therefore, to try BCG vaccination en masse. It is the cheapest and only measure within our means."

I suggest that it is not "reasonable" to substitute a remedy of doubtful effectiveness, an unknown quantity, for the tried and proved remedy because the latter is "too expensive". No doctor would consider such an approach in dealing with a patient. When a patient suffers from an operable malignancy, the doctor must insist upon the necessity of the operation. To encourage such a patient to have faith in an antibiotic because he could not afford the operation would be dereliction of duty. Yet that is exactly what we do as public health officers.

It is our obligation to describe the methods necessary to the accomplishment of the objective, the elimination of tuberculosis, and then to administer the outlined program to the full extent permitted by the funds made available. We are not legislators, calculating on the basis of what is legislatively desirable. It is generally agreed that a broad program of public health is the surest and, in the long run, the quickest way to achieve our objective. It is our duty to insist upon this fundamental fact without compromise and without allowing the problem to be obscured by unproved short-cuts. Many years ago Professor Vaughan of Ann Arbor said concerning tuberculosis in the Philippines:

"I went through your tenement districts yesterday and I want to say quite emphatically that as long as such districts continue in your city and in your country, you are not likely to get rid of tuberculosis. I went up to a house and I found there was no light except that which came through the doorway. I went to the kitchen, and I saw the conditions under which the food was prepared. I want to say frankly that I do not believe that you can do very much in the eradication of tuberculosis in this country as long as such tenement houses exist."

There is no evidence at this time that BCG fundamentally alters Dr. Vaughan's analysis. Poverty is still the problem. BCG can only waste money, however, little, that might otherwise be used to combat the disease at its root, and it can only encourage laymen in the false conviction that

a short-cut can be found. In view of the knowledge available about BCG, any public health agency which considers making specific recommendations for a mass BCG program assumes a large responsibility.

### SUMMARY

1) During a recent five year period, 1,000,000 persons in the Philippines were examined and approximately 9 per cent were found to be suffering from tuberculosis. While this is probably a higher percentage than exists throughout the Islands, it is a reasonably good criterion of the magnitude of our problem.

2) When these cases were found, facilities were not available for isolation or adequate treatment so they remained free to continue spreading infection. It was not even possible to provide medicine and supplementary food for them.

3) BCG had previously been used in the Philippines on a small scale but without impressive results. However, it was suggested and strongly encouraged by the World Health Organization as the method of solving the problem.

4) BCG has become the official tuberculosis control program and has absorbed a great share of the financial resources available to combat tuberculosis.

5) Nowhere has the effectiveness of BCG been placed beyond dispute. Authorities on tuberculosis remain unconvinced of its value. Opponents of BCG are asked for the time being to stop being men of science but to accept this vaccine without the rigorous demonstration of its harmlessness and effectiveness that are demanded of other medical preparations.

6) BCG has not proved itself elsewhere and there is no reason to anticipate that it will do so in the Philippines. It can only waste money that might otherwise be used to combat the disease at its roots and it can only encourage laymen in the false conviction that a short-cut can be found.

7) The only program that offers any promise of controlling tuberculosis in the Philippines consists of nation-wide education, sanitation, hospital construction for isolation simultaneous with case finding and a vigorous government program directed to improvement of the standards of living. Until these measures are undertaken, tuberculosis will remain with us as a serious public health problem, BCG or no. It is our duty to insist upon the fundamental program so successfully employed elsewhere and to avoid unproved short-cuts.

### RESUMEN

1) Durante el último período reciente de cinco años se examinaron 1,000,000 de personas en las Filipinas y aproximadamente se encontró que 9 por ciento sufrían tuberculosis. Si bien este es un porcentaje más alto que el que existe en todas las Islas, es un criterio razonable para estimar la magnitud del problema.

2) Cuando se encontraron estos casos, no había facilidades para el aislamiento o el tratamiento adecuado, de manera que continuaron disemi-

nando la infección. Aun el proveerlos de medicinas y alimentación suplementaria no fué posible.

3) El BCG, se había usado previamente en pequeña escala, pero sin resultados impresionantes. Sin embargo, su empleo fué sugerido y fué alentado por la organización Mundial de la Salud, como el método adecuado para resolver el problema.

4) El BCG, ha venido a ser el método oficial para dominar la tuberculosis y ha absorbido una gran parte de los recursos financieros existentes para combatir la tuberculosis.

5) En ninguna parte se ha demostrado la efectividad del BCG. Las autoridades en tuberculosis permanecen no convencidas de su valor. A los opositores del BCG, se les ha pedido que por el momento dejen de ser hombres de ciencia y que acepten esta vacuna sin la rigurosa demostración de inocuidad y efectividad que se piden a otras preparaciones médicas.

6) El BCG, no ha dado pruebas de eficacia en otras partes y no hay razón para prever que así resulte en las Filipinas. Sólo puede consumir el dinero que podría emplearse de otra manera para erradicar la enfermedad y puede sólo alentar a las personas fuera de la profesión en la convicción falsa de que puede encontrarse un camino más directo.

7) El único plan que ofrece alguna promesa de dominar la tuberculosis en las Filipinas, consiste en la educación amplia, la mejoría sanitaria, la construcción de hospitales para el aislamiento simultáneo con el descubrimiento de los casos y un plan de gobierno tendente a la mejoría del nivel de la vida.

Hasta que estas medidas se pongan en práctica, la tuberculosis permanecerá entre nosotros como un serio problema de la salubridad, ya se use el BCG o no. Es nuestro deber insistir sobre el plan fundamental tan satisfactoriamente empleado en otras partes y evitar no demostrados caminos breves hacia la meta.

## RESUME

1) Pendant ces cinq dernières années, 1,000,000 d'individus ont été examinés aux Philippines et on dénombré parmi eux environ 9% de tuberculeux. Bien que ce pourcentage soit probablement plus élevé que celui de l'ensemble des îles, il représente legiquement un bon critère de l'amplitude du problème.

2) Après l'identification de ces cas, il n'a pas été possible de leur donner les facilités d'isolement ou de traitement et ils persistèrent à semer la contagion. Il n'a même pas été possible de leur accorder des médications et un supplément de nourriture.

3) Le B.C.G. a été utilisé précédemment aux Philippines sur une petite échelle, mais sans résultats impressionnants. Toutefois, il a été conseillé et fortement encouragé par l'Organisation Mondiale de la Santé comme le procédé susceptible de résoudre la question.

4) La vaccination par le B.C.G. est devenue le programme officiel de la lutte contre la tuberculose et a absorbé une grande part des ressources attribuées à cette lutte.

5) Nulle part le B.C.G. n'a été considéré comme ayant une efficacité indiscutable. Des personnes qui font autorité en phthisiologie n'ont pas été convaincues de sa valeur. On demande à ceux qui s'opposent à la pratique du B.C.G. de cesser pour l'instant d'être des hommes de science et d'accepter ce vaccin sans avoir la démonstration d'innocuité et d'efficacité que l'on demande aux autres produits.

6) Le B.C.G. n'a fait, en aucun autre lieu, le preuve de son efficacité et il n'y a aucune raison d'imaginer qu'il en sera autrement aux Philippines. Il ne servira qu'à gâcher les ressources pécuniaires qui auraient pu d'une autre façon être utilisées à s'attaquer aux racines du mal. Il ne servira qu'à répandre la fausse conviction qu'il est capable de simplifier la lutte contre la tuberculose.

7) Le seul programme qui offre quelque espoir de vaincre la tuberculose aux Philippines consiste en une éducation sanitaire étendue, en la construction d'hôpitaux permettant l'isolement des malades à mesure qu'on les dépiste et en une action gouvernementale énergique pour l'amélioration du standard de vie. Tant que ces mesures n'aurent pas été mises en route, la tuberculose restera un grave problème de santé publique, qu'on utilise le B.C.G. ou qu'on ne l'utilise pas. L'auteur considère que son devoir est d'insister sur le programme fondamental qu'il estime avoir été la cause des succès obtenus dans les autres pays et d'éviter l'utilisation de procédés dont l'efficacité n'a pas été démontrée.

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# Multiple Puncture and Intradermal BCG Vaccination

## A Quantitative Comparison in Terms of Allergy Production

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In the many mass BCG vaccination campaigns conducted by the International Tuberculosis Campaign during 1948-51,<sup>1</sup> only the intradermal (I.D.) method was used; extensive experience was accumulated about the practicability of the method and level of post-vaccination allergy produced. However, when the Philippine Department of Health, with the assistance of WHO and UNICEF, started a nation-wide BCG vaccination campaign in October 1952, the multiple puncture (M.P.) method was selected for various reasons as the method of choice.

It was S. R. Rosenthal<sup>2</sup> who, in 1939, described and developed the M.P. method of giving BCG vaccine and reported that satisfactory post-vaccination tuberculin allergy could be obtained with this technique. A good many other investigators have subsequently used this method and reported varying conversion rates. One quantitative study of the allergy resulting from multiple puncture vaccination was performed by the United States Public Health Service,<sup>3</sup> but no direct quantitative comparison of the multiple puncture and intradermal methods of vaccination, in terms of post-vaccination tuberculin allergy, was found in the available literature.

The present study was therefore designed to measure and compare the level of post-vaccination allergy obtained by giving the same batch of vaccine intradermally and by multiple puncture to comparable groups of school children.

### *Material and Methods*

The pupils in the three largest public elementary schools in Manaoag Municipality comprised the study. Manaoag is situated in Pangasinan Province, a densely populated, tropical lowland of rural character in the central part of Luzon, the main island of the Philippines.

The three schools had a total enrollment of 3,034 pupils. Those present on the days of pre-vaccination testing, October 7 to 9, 1952—altogether 2,632 children (1,213 boys and 1,419 girls, aged 5 to 17 years), were given a tuberculin test with 5 TU (0.0001 mg. in 0.1 ml.) injected intradermally. The tuberculin dilution was prepared in the Philippine BCG Laboratory from a stock solution of PPD (RT XXII) sent from the State Serum Institute in Copenhagen, Denmark. (The same dilution was used for all pupils given pre-vaccination tuberculin tests in this study.)

All reactions were read at 72 hours. The site of the test was carefully palpated and the transverse diameter of the perceptible induration measured with a millimeter ruler. Only persons with indurations of less than 6 mm. in diameter were considered eligible for vaccination.

The vaccine was given alternately by the intradermal and by the multiple

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puncture method as the children came down the line to be vaccinated. This rotation system was used to eliminate bias in the allocation of non-reactors to the two vaccination techniques. Hence, the results could be compared with a reasonable degree of assurance that differences in post-vaccination allergy, if any, would be due to the vaccination technique and not to systematic differences between the two groups of children.

The BCG vaccine used in the study was produced by the Philippine BCG Laboratory in Alabang. The vaccine for intradermal injection was prepared to contain 1 mg. BCG/ml. and for multiple puncture 20 mg./ml. Both vaccines were prepared from the same harvest of BCG (Batch No. 102) and stored under the same conditions until the moment of vaccination. The vaccines were used within two weeks after harvest.

The techniques of vaccination were as follows:

a) *Intradermal Method*: 0.1 ml. of vaccine was injected as superficially as possible into the skin of the left deltoid region. The skin was not cleansed before the injection.

b) *Multiple Puncture Method*: A modified Rosenthal method was used. The skin was not cleansed before vaccination. One drop of the vaccine was pipetted onto the skin of the left deltoid region. The drop was smeared out over an area of about 2 by 4 cm. The skin on this area was then perforated (40 punctures in four rows of 10 each) with a straight surgical sewing needle. For each puncture the needle was held tangentially to the skin and its point inserted into the skin. An upward movement was then made without withdrawing the needle to ensure that the needle penetrated the upper layer of the skin.

The personnel in the team consisted of Dr. Arsenio Serquina and Mrs. Rosa R. Ocximer from the Philippine National Chest Center, Manila, and the writer. Dr. Serquina and Mrs. Ocximer performed all the pre- and post-vaccination tuberculin testing, and the writer read all the reactions. Dr. Serquina gave the intradermal and Mrs. Ocximer the multiple puncture vaccinations.

The type of vaccination and the giving and reading of tuberculin tests were recorded on an individual record card for each child. For purposes of identification each card also gave the name, age and sex of the child as well as name of school, teacher and grade.

Sixteen weeks after vaccination (January 26 to 30, 1953) the team returned to the three schools to give intradermal 5 TU tuberculin tests to the vaccinated children. The tuberculin dilution was prepared by the laboratory in Alabang from the same lot of stock solution that had been used for the pre-vaccination tuberculin testing. The reactions were again read at 72 hours, and the work was arranged so that the reader, when reading the tuberculin reactions, could not know what method of vaccination had been used for each child. This was done in order to exclude any bias deriving from the reader's expecting or hoping for a certain difference in the size of post-vaccination reactions between the two groups.

The total number of pupils tested, vaccinated and retested is given in the following table by school and method of vaccination:

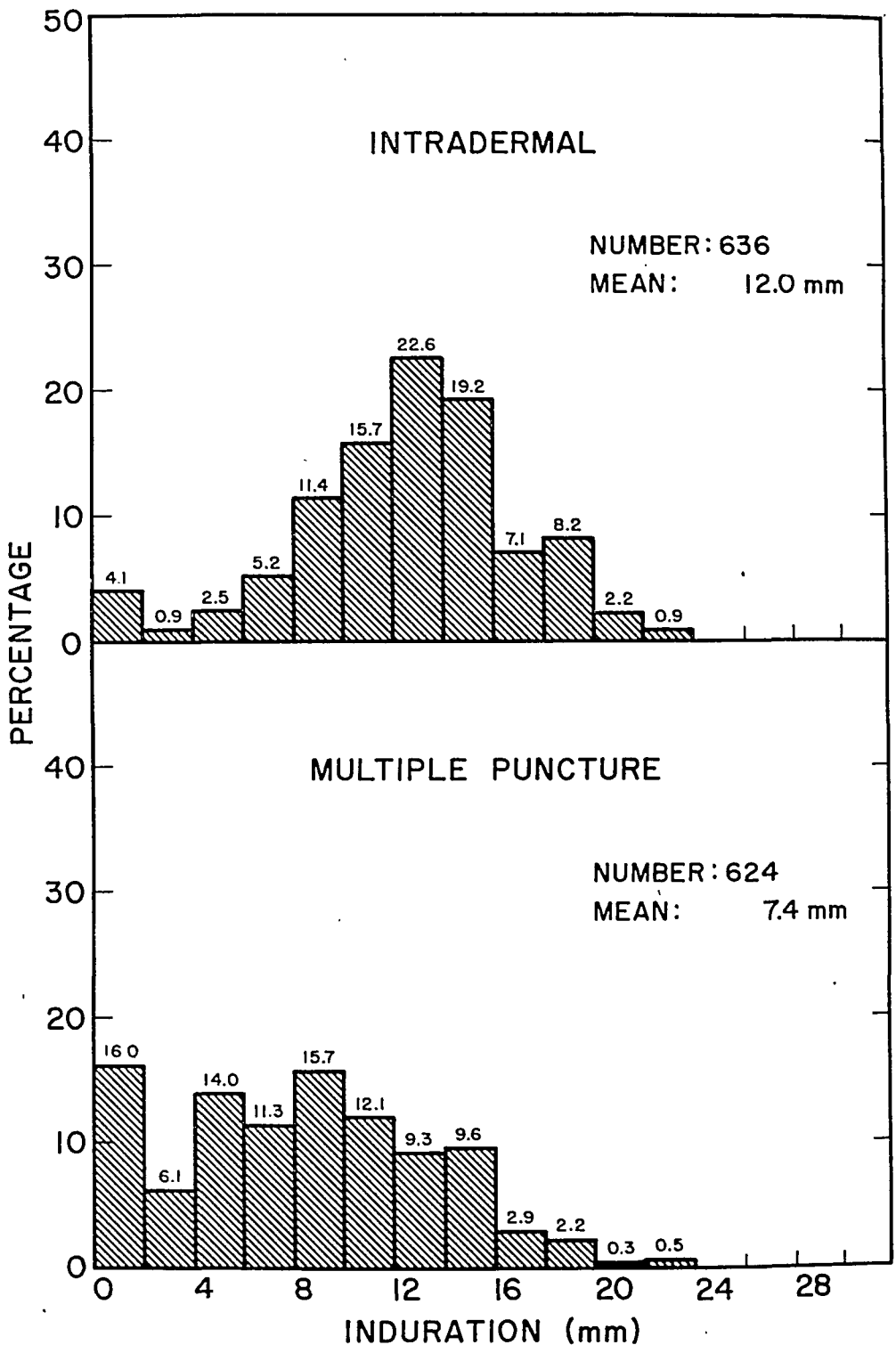


FIGURE 1: Frequency distributions by size of reactions to intradermal 5 TU tuberculin tests in school children 16 weeks after vaccination intradermally (upper section), or by multiple puncture (lower section). —Manaoag Municipality, Pangasinan Province, Philippines, January 1953.

Name of School	Enrollment	Pre-vacc. Test	Vaccinated		Post-vacc. Test	
			I.D.	M.P.	I.D.	M.P.
Manaoag Cent. School	1703	1548	486	484	387	383
Laoac Elem. School	734	612	229	227	141	137
Cabanban Elem School	597	472	160	168	108	104
TOTAL	3034	2632	875	879	636	624

The figures for the pre- and post-vaccination testing include only the children who completed the test, i.e. who returned for the reading of the test.

### Results

#### *Post-vaccination Tuberculin Allergy:*

The level of tuberculin allergy in each of the two groups appears from the frequency histograms in Figure 1 giving the distribution by size of induration to Mantoux 5 TU of the 636 children vaccinated by the intradermal and the 624 vaccinated by the multiple puncture method.

For the group vaccinated intradermally, reactions measuring 12 to 13 mm. are most frequent, and nearly 60 per cent of all reactions are between 10 and 16 mm. in diameter. For the group vaccinated by the multiple puncture method there is no modal point: the reactions are spread fairly uniformly over a range of 0 to 16 mm. The mean size of reactions is 12.0 mm. for the intradermal group, with about 93 per cent measuring 6 or more mm. in diameter, compared with a mean of 7.4 mm. for the multiple puncture group and only about 64 per cent measuring 6 or more mm. in diameter.

Another difference between the two distributions is the high frequency (16 per cent) of persons with little or no perceptible induration (recorded as "0" or "1" mm.) in the group vaccinated by the multiple puncture method in contrast to only 4.1 per cent in the group vaccinated intradermally.

The frequency of small reactions, those measuring from 0 to a few millimeters, is not correlated with age: the proportion of small reactions is about the same for all ages in the present material.

#### *Pre-vaccination Tuberculin Allergy:*

The frequency distribution by diameter of induration of the pre-vaccination 5 TU tuberculin reactions is shown in the upper section of Figure 2. Ordinarily distributions by size of pre-vaccination tuberculin reactions (to 5 or 10 TU) show a concentration of the reactions into two rather distinct groups—one of small and zero reactions (the non-infected) and one of fairly large reactions (the infected). In the present distribution, however, no clear separation is apparent.

A way to interpret the pattern of tuberculin sensitivity shown in the figure is suggested by comparison with a similar pattern found with 5 TU tests in Madanapalle, South India, by teams from the Field Research Station of the WHO Tuberculosis Research Office.<sup>4</sup> The results in India were interpreted on the basis of extensive studies in different countries as indicating the presence of three groups in the population: one group with little



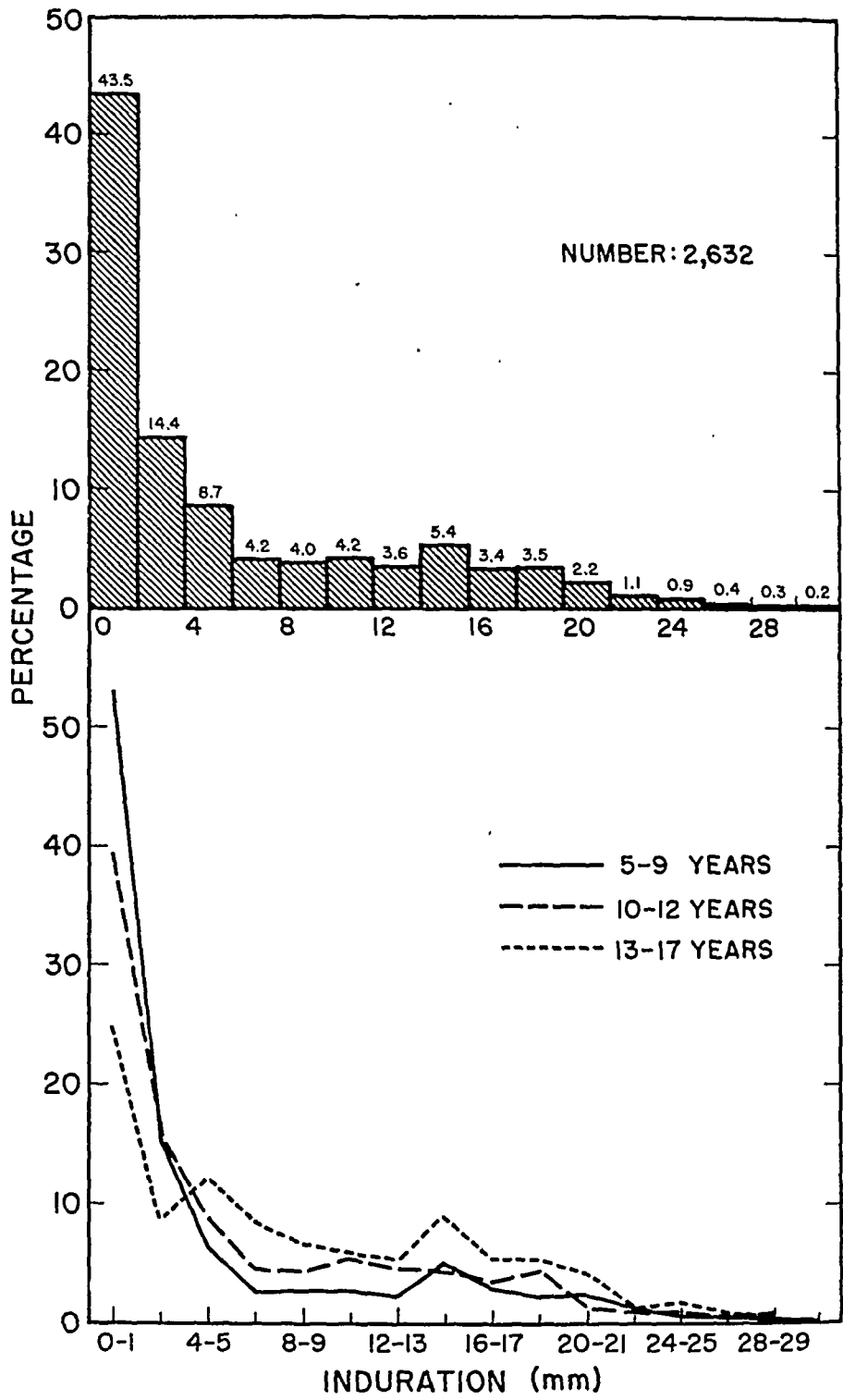


FIGURE 2: Frequency distributions by size of reactions to intradermal 5 TU tuberculin tests in school children, for all ages (upper section), and for three age groups (lower section). —Manaoag Municipality, Pangasinan Province, Philippines, October 1952.

or no reaction, the non-infected; one group with large reactions, the infected; and an intermediate group with a low-grade kind of sensitivity of non-specific origin, i.e. not specific for tuberculous infection. The usual separation of infected from non-infected was thus obscured by interposition of the group with low-grade sensitivity, resulting in a distribution in which the separate segments could not be easily distinguished.

The present findings might be interpreted in the same way. Inspection of Figure 2 reveals at least some concentration of large reactions 14 to 15 mm. in diameter, probably the modal point for the group with the high-grade kind of sensitivity commonly associated with specific tuberculous infection. Separating the study population according to age, as in the lower section of the figure, tends to support this interpretation: the frequency of strong reactions increases with age but there is no apparent change in the form or position of a modal group centering around 14-15 mm.

Assuming, for the moment, that the level of allergy produced by natural infection averages around 14 to 15 mm. to the 5 TU test, one may then have a basis for evaluating the level of allergy produced by BCG vaccination in this study. With the intradermal method, the level of BCG-induced allergy four months after vaccination was nearly as high as that produced by natural infection. With the modified multiple puncture method used, the level was considerably lower.

As the results of the present study clearly showed that a higher degree of tuberculin allergy resulted from intradermal BCG vaccination than from multiple puncture, the intradermal method was used for the mass BCG vaccination campaign in the Philippines.

### *Discussion*

The tuberculin reactions of the children vaccinated by multiple puncture in this study averaged 5 mm. smaller than those vaccinated intradermally. From field investigations of the quantitative effect on post-vaccination allergy of serial dilutions of BCG vaccine,<sup>5</sup> it may be estimated that a difference of 5 mm. in mean reaction size reflects a 10 to 100 fold difference in dose. Thus, the children vaccinated intradermally in the present study may have received, in effect, a dose of BCG at least 10 times larger than the children vaccinated by multiple puncture.

Rosenthal has recently recommended that the strength of the liquid vaccine used for vaccination by the multiple puncture method (30 to 36 punctures) should be raised from 15-20 mg./ml. to 35 mg./ml.<sup>6</sup> As previously mentioned, the strength of vaccine we used was 20 mg./ml. Although our material can furnish little information on the point, it would seem unlikely that our results with multiple puncture would have been appreciably affected had we used the higher dose.

Apart from the matter of dosage, the question of the effect of exposing vaccine to light should also be considered, as it is now recognized that BCG organisms are rapidly killed by light. As vaccination by multiple puncture may involve both a longer and a more intense exposure of vaccine during as well as immediately after vaccination, it is possible that at least part

of the difference in results between the two methods used here might be accounted for in this way. This phenomenon is, however, not likely to have accounted for much of the difference as all vaccinations in the present study were carried out in the shade, never in direct sunlight. In this connection the difference in time of giving an intradermal and a multiple puncture vaccination was negligible (less than one minute), and most of the children covered their shoulders with blouse or shirt sleeves after vaccination.

### SUMMARY

The present study was set up in connection with the WHO/UNICEF-assisted BCG vaccination campaign in the Philippines in order to measure and compare the degree of tuberculin sensitivity produced by the intradermal and by a modified multiple puncture method of vaccination.

In Manoag Municipality, 2,632 school children were given an intradermal tuberculin test with 0.0001 mg. of PPD (Mantoux 5 TU) and the 1,754 non-reactors to this test were given BCG vaccine alternately by the intradermal and the multiple puncture methods. Sixteen weeks later the vaccinated children were retested with 5 TU. In reading the reactions, precautions were taken to assure that the reader could not know which method of vaccination had been used in each child.

The tuberculin reactions of children vaccinated intradermally averaged 12.0 mm. in diameter—a level of allergy almost as high as that produced by natural infection: the tuberculin reactions of children vaccinated by multiple puncture averaged only 7.4 mm. in diameter. As a result of this study, intradermal vaccination replaced the multiple puncture method for the mass BCG campaign in the Philippines.

Grateful acknowledgment is made to Dr. Sixto A. Francisco, Chief of the Tuberculosis Division, Philippine Department of Health and members of his staff, whose interest and assistance made the present field work possible; and to the staff of the WHO Tuberculosis Research Office, Copenhagen, for critical comments and help in preparing the paper.

### RESUMEN

Este estudio se realizó en conexión con la WHO-UNICEF que ayudó a la vacunación con BCG en Filipinas para medir y comparar el grado de sensibilidad tuberculínica producidas por la vía intradérmica y por un método modificado de la múltiple puntura.

En la municipalidad de Manoag se aplicó a 2,632 niños escolares una dosis de 0.0001 mg. de PPD (Mantoux 5 TU) y a los 1,754 de éstos que resultaron negativos a esa prueba, se les aplicó BCG tanto por la vía intradérmica, como por puntura dérmica en casos alternados.

Dieciseis semanas después, los niños vacunados fueron otra vez sujetos a la prueba con 5 TU. En la lectura de las reacciones se tuvo cuidado para asegurarse de que el observador no pudiese conocer qué método se había usado en cada niño.

Las reacciones tuberculínicas en los niños vacunados intradérmicamente,

dieron una dimensión media de 12 milímetros de diámetro, un nivel de alergia casi tan elevado como el producido por la infección natural; las reacciones tuberculínicas en los niños vacunados por puntura múltiple, sólo daban una media de 7.4 mm. de diámetro.

Como resultado de este estudio, la vacunación intradérmica substituyó a la puntura múltiple en la campaña de vacunación en masa por el BCG en las Filipinas.

### RESUME

Ce travail à été établi en relation avec la campagne de B.C.G. organisée aux Philippines par l'O.M.S. et l'UNICEF. Son objet est de mesurer et de comparer le degré des réactions tuberculínicas obtenues par vaccination, en comparant la voie intradermique et une méthode modifiée des piqûres multiples.

Dans la ville de Manoag, 2,632 écoliers furent soumis à une inoculation intra-dermique de tuberculine, dosée à 0.01 milligramme de tuberculine purifiée (ou dosée à cinq unités). Les 1,754 enfants dont les réactions furent négatives, furent vaccinés par le B.C.G., les uns par voie intradermiques, les autres par la méthode des piqûres multiples. Seize semaines plus tard, les enfants qui avaient été vaccinés furent de nouveau soumis à la réaction tuberculínicque avec une dose de cinq unités de tuberculine. Pour la lecture des réactions, toutes les précautions avaient été prises afin de s'assurer que ceux qui étaient chargés de les préciser n'avaient pas pu prendre connaissance de la méthode qui avait été utilisée pour chaque enfant.

Les réactions tuberculínicas des enfants vaccinés par voie intra-dermique présentèrent en moyenne un diamètre de 12 millimètres, ce qui implique une allergie environ aussi élevée que celle produite par l'infection naturelle. Des réactions tuberculínicas des enfants vaccinés par la méthode des piqûres multiples ne donnèrent en moyenne que des réactions de 7 mm., 4 de diamètre. A la suite de cette étude, pour la vaccination collective par le B.C.G. dans les Philippines, on a remplacé la méthode des piqûres multiples par la vaccination intra-dermique.

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# Serial Chest Roentgenograms: An Evaluation\*

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Many pulmonary diseases have long periods of latency and therefore go unrecognized until symptoms become manifest. Failure to apply techniques for early recognition of such abnormalities may result in unduly long periods of treatment, chronic invalidism, or hopeless prognosis.

The simplest way of detecting most early pulmonary disease is by roentgenographic study of the chest. This method of case-finding is more effective if these studies are repeated at intervals. The availability of previous roentgenograms for comparison enhances the reliability of interpretations and illuminates the whole controversial matter of the accuracy of readings based on single films.<sup>1</sup>

Serial chest x-ray films have been available on Philadelphia foodhandlers since January 13, 1947, when the City provided a photofluorographic unit for the annual chest x-ray films which had just been made mandatory for this group of workers. About 55,000 Philadelphians report to this unit annually and, of these, 40,000 to 45,000 are foodhandlers. Almost two-thirds of the foodhandlers are reporting back, having been x-rayed at least once previously.

The first screening yields about 2 per cent with possible tuberculosis. This figure is a little higher than that reported for many surveys because our photofluorograms are over-read by policy.<sup>2</sup> We believe it is better to err on the side of over-reading than to give false reassurance. This plan was inaugurated because we feel that surveys are screening processes rather than diagnostic procedures.

Routine clinical follow-up after the initial photofluorograms results in a diagnosis of active tuberculosis in about one-half of one per cent, which is in accordance with survey follow-up findings in general.

The shifts from negative to possibly tuberculous on re-x-ray run slightly under half of one per cent. Less than half of these impress the radiologist as probably active tuberculosis. The others are interpreted either as of indeterminate activity or are inactive on the basis of retrospective review.

The following case represents the ideal results obtainable when a chest film reveals active tuberculosis within one year of a negative x-ray film and diagnosis, hospitalization, and good therapy are provided promptly:

*Case 1:* J.C., a 55 year old white bartender, had a negative photofluorogram February 20, 1948 (Figure 1A). Eleven months later, January 21, 1949 (Figure 1B), his photofluorogram was read: "Moderately advanced active tuberculosis: Infiltra-

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tions in the left infraclavicular region." This man was a diabetic who felt quite well. He had no fatigue, cough, sputum, hemoptysis nor contact with tuberculosis. However, he had lost 35 pounds during the previous 14 months. Positive sputum was obtained on February 9, 1949. Hospitalization was effected on March 9, 1949, and shortly thereafter pneumothorax was induced. Sputum became negative by April 1, 1949. He is well and working with left pneumothorax. His sputum has continued to be negative.

While such excellent results are possible when tuberculosis is found in an early phase, they can only be anticipated if hospital facilities are available and immediate appropriate therapy is inaugurated. The following foodhandler had had two negative photofluorograms before the one which revealed acute tuberculosis. Despite the fact that his tuberculosis was found before he became symptomatic, he died at home without therapy seven months after having been listed for a hospital bed.



FIGURE 1A

FIGURE 1B

*Figure 1A, Case 1: February 20, 1948. Negative.—Figure 1B, Case 1: January 21, 1949. Infiltrations in the left Infraclavicular region. Sputum positive.*

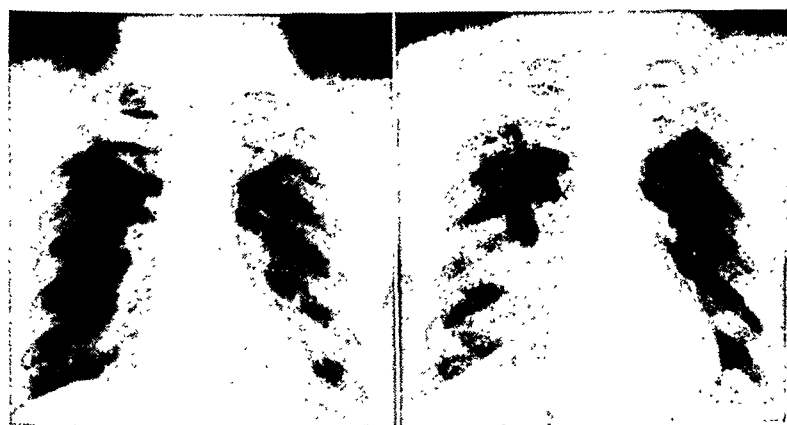


FIGURE 2A

FIGURE 2B

*Figure 2A, Case 2: March 18, 1948. Negative.—Figure 2B, Case 2: June 30, 1949. Dense infiltrations below right mid-lung. Sputum positive.*

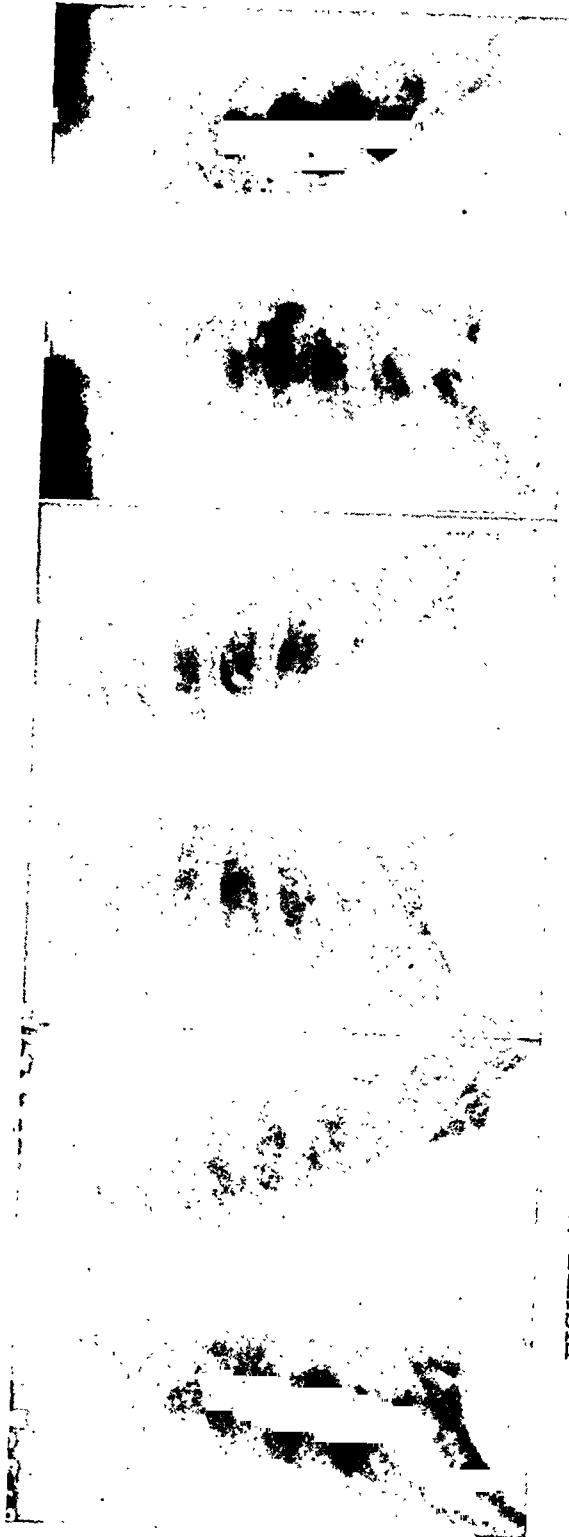


FIGURE 4A

FIGURE 4B

FIGURE 4C

*Figure 4A, Case 5: November 25, 1947. Photofluorogram interpreted as "negative."*  
*Retrospective review reveals lesion below right hilum.*  
*Figure 4B, Case 5: February 4, 1949. Mass below right hilum. No symptoms present.*  
*Figure 4C, Case 5: May 21, 1951. Mass below right hilum larger. No symptoms present. Hamartoma removed August 3, 1951.*

*Case 2:* G.W.D., a 47 year old Negro dishwasher, had negative photofluorograms on May 27, 1947, and March 18, 1948 (Figure 2A). On June 30, 1949 (Figure 2B), he had "dense infiltrations below the right mid-lung." No symptoms were present. Positive sputum was not obtained until August 29, 1949. He was listed for hospitalization September 9, 1949, but was never admitted nor treated while awaiting a bed. He died at home April 9, 1950.

Early case-finding can be the magic key to tuberculosis control only if beds for treatment are available. A compromise program of home treatment should be inaugurated while awaiting hospitalization in those localities where bed shortages exist.

The presence of pleural effusion following negative photofluorograms is always highly significant. If it is right-sided and associated with cardiac enlargement, the diagnosis is fairly obvious. If the cardiac shadow is normal, it must be considered tuberculous until proved otherwise. The following two cases are presented as contrasts—the first having received ideal treatment for tuberculous effusion, the second having received inadequate therapy. Obviously, the value of the survey is only as good as the calibre of the subsequent treatment.

*Case 3:* J.M.G., a 21 year old Negro bus boy, had a negative photofluorogram March 5, 1948. The July 6, 1949 retake revealed a massive right pleural effusion. He was hospitalized July 18, 1949. Re-ray two months after admission revealed left pleural effusion as well as the involvement on the right. Tubercle bacilli were not cultured from the pleural fluid. He was discharged May 8, 1951, to a rehabilitation centre. On January 16, 1952, he reported back for routine check-up. The fluid on the right had completely absorbed and there was only a small amount of residual pleural thickening on the left.

He had long-term adequate treatment. The follow-up picture when treatment is inadequate is illustrated by the following:

*Case 4:* C.M., a 25 year old Negro porter, had a negative photofluorogram November 24, 1947 (Figure 3A). Two years later, November 3, 1949 (Figure 3B), he had left pleural effusion. Recognizing the gravity of the situation in a young



FIGURE 3A

FIGURE 3B

*Figure 3A, Case 4: November 24, 1947. Negative.*

*Figure 3B, Case 4: November 3, 1949. Left pleural effusion.*



Negro, immediate hospitalization was arranged. Tubercle bacilli were never isolated from the pleural fluid but streptomycin was given for two and one-half months. He was discharged after only three and one-half months of hospitalization. He was found to be working in a Philadelphia hospital shortly after discharge. This hospital was notified of our concern over the young man's inadequate treatment. X-ray films January 4, 1951, and June 7, 1951, at the hospital showed only thickened pleura but in September, 1951, about two years post-effusion, he developed a large fluctuant mass over the right posterior chest. Material obtained from this area by aspiration yielded tubercle bacilli. The right ninth rib was resected and showed tuberculous osteomyelitis.

This sequence of events is not rare following inadequately treated tuberculous effusion. The experience of the armed forces yielded ample evidence to this effect.<sup>3</sup>

The problems of differential diagnosis are legion. Not only is there the question of etiology but the natural history of tumor growth, suppurative disease, tuberculosis, sarcoid, and other pulmonary diseases unfolds like a panorama before the eyes of the survey reader. The development of pathologic change in patients is demonstrated by the following case in which a "negative" photofluorogram was followed by the appearance of a mass subsequently proved to be a benign tumor. He refused surgery at first until a definite increase in the size of the neoplasm was demonstrated. The period of observation extended over three and one-half years.

*Case 5:* T.C., a 49 year old white bartender had a photofluorogram interpreted as negative November 25, 1947 (Figure 4A). In retrospect a lesion below the right hilum is visible. On February 4, 1949 (Figure 4B), a round mass was seen below the right hilum. He was asymptomatic and refused the chest clinic's recommendation of hospitalization for diagnosis and treatment. On April 13, 1950, there was doubt as to whether the mass was larger. On May 21, 1951 (Figure 4C), the annual photofluorogram revealed a definite increase in size and the man was persuaded to enter the hospital for surgery. The lesion was a hamartoma.

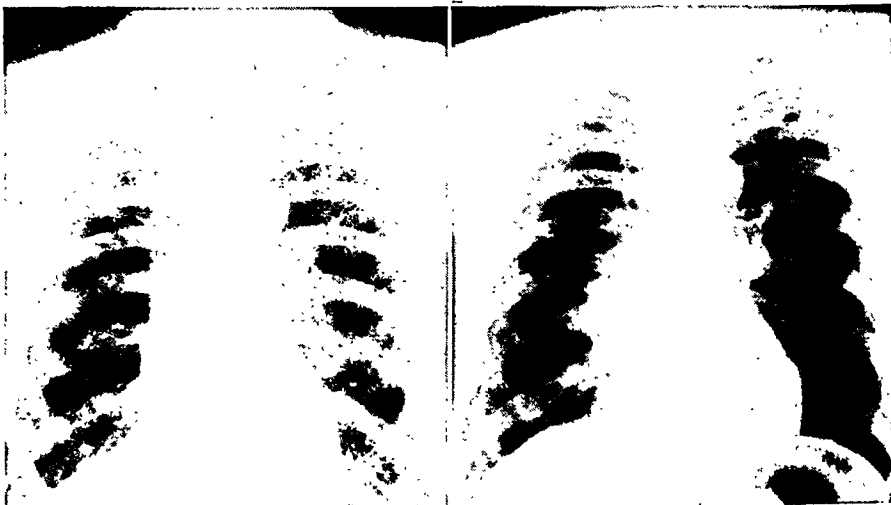


FIGURE 5A

FIGURE 5B

*Figure 5A, Case 6:* April 25, 1947. "Negative." In retrospect there is a questionable rounded density below the right hilum.

*Figure 5B, Case 6:* April 29, 1948. Mass below right hilum.

Because of the discouraging survival rates in lung cancer, it seems worth while to examine this situation in some detail. There were 49 proved primary bronchogenic carcinomas among 247,060 satisfactory photofluorograms exposed between May 2, 1947, and December 31, 1951. While this represents only two cases per 10,000 individuals, the prevalence for men over 45 was eight cases per 10,000 (38 among 45,887).

It is of interest to note that 30 of the proved cancers had been found on initial photofluorography. Nineteen had had previous photofluorograms read as negative. In retrospect, only 10 of these 19 were truly negative, the balance having had small shadows that had been overlooked. The resectability and survival of these three groups are as follows:



FIGURE 6A

FIGURE 6B

*Figure 6A, Case 7: September 16, 1950. Essentially negative except for increased basal markings and a calcified nodule at the right third anterior rib.*

*Figure 6B, Case 7: September 13, 1951. Partial atelectasis left lung. Inoperable. Died October 24, 1951.*

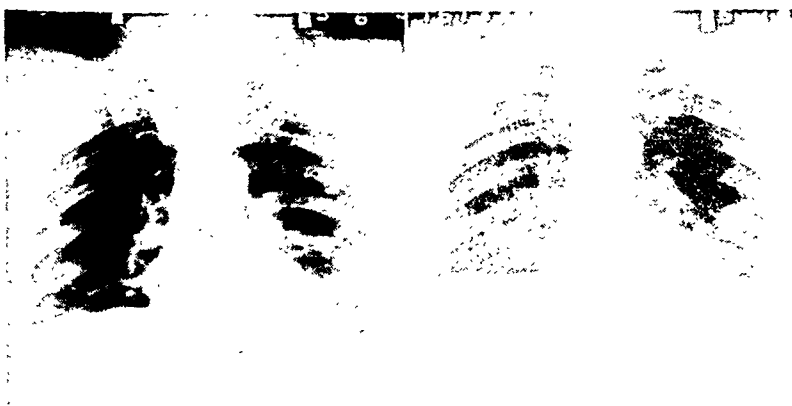
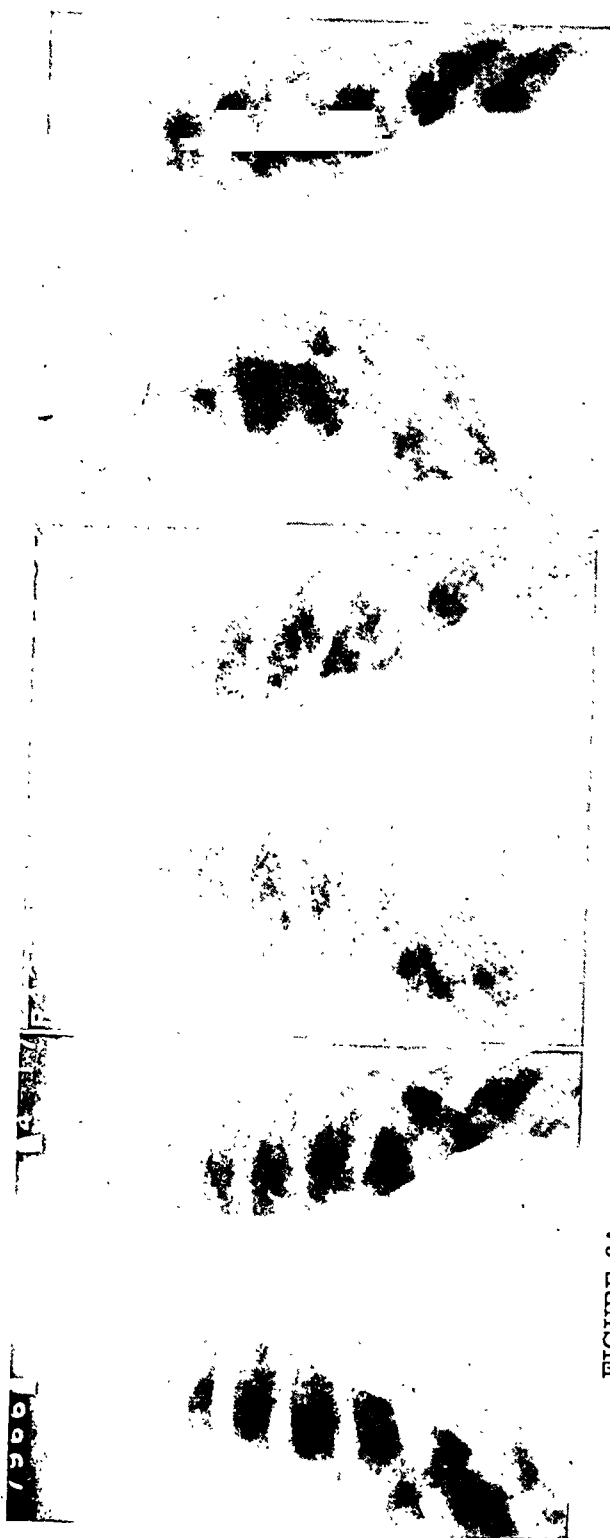


FIGURE 7A

FIGURE 7B

*Figure 7A, Case 9: May 6, 1947. Negative.*

*Figure 7B, Case 9: May 18, 1949. Mass left base.*

**FIGURE 8A****FIGURE 8B****FIGURE 8C**

*Figure 8A, Case 10: April 17, 1947. The lesion is present at the level of the third anterior rib.*

*Figure 8B, Case 10: January 23, 1948. Mass at right second anterior rib (missed by survey reader).*

*Figure 8C, Case 10: May 28, 1952. Volume shrinkage of right upper lobe.*

I. Those with abnormalities on initial photofluorogram . . . . .	30
Resected . . . . .	8
Living 13 months after resection . . . . .	1
II. Those with previous photofluorograms read negative and considered negative even on retrospective review . . . . .	10
Resected . . . . .	4
Living eight months after resection . . . . .	1
III. Those with previous photofluorograms read negative but considered abnormal on retrospective review . . . . .	9
Resected . . . . .	5
Living 18 to 45 months after resection . . . . .	3

It is of interest to note that half of those with available earlier photofluorograms had resectable lesions in contrast to only a quarter of those without previous films. So far as survival is concerned, the study is too recent for evaluation but the advantage of previously "negative" chest x-ray films is apparent when one realizes that five of 19 such individuals are living in contrast to only one of 30 without available previous films.

The following foodhandler, reporting for re-ray one year after a negative photofluorogram, was found to have a mass later proved to be bronchogenic carcinoma. He has survived four years after right pneumonectomy.

*Case 6: C.Y.*, a 55 year old oriental cook, had a "negative" photofluorogram on April 25, 1947 (Figure 5A). In retrospect there is a questionable rounded density below the right hilum. One year later, April 29, 1948 (Figure 5B), a large mass was found below the right hilum. Upon interview May 11, 1948, the only symptom was cough which had been present for years. There was no notation made as to whether there had been recent change in the character of the cough. The man was referred to a chest clinic where he underwent routine examination. After considerable difficulty, he was finally persuaded to enter a hospital on August 16, 1948. The right lung was resected September 9, 1948. He was discharged September 22, 1948. Histologically, the tumor was a squamous cell carcinoma. The patient has returned annually for photofluorograms. The residual lung remains clear and the man continues to work as a cook.

While it is too early to view this as a cure, the case nevertheless presents convincing evidence of the value of periodic chest x-ray films.

On the other hand, the following case highlights the fact that centrally located lung cancers may be silent clinically and negative by routine roentgenography until they are so far advanced as to be inoperable.

*Case 7: P.N.*, a 68 year old white laborer, was referred for photofluorography September 16, 1950 (Figure 6A), by his private physician. The miniature film was essentially negative except for increased basal markings and a calcified nodule at the right third anterior rib. One year later, September 13, 1951 (Figure 6B), he was sent back to the unit by another physician because he had had "pneumonia" of one month's duration. This time there was atelectasis with a shift of the entire mediastinum into the left chest. He was hospitalized October 5, 1951. Bronchoscopy revealed an ulcerating tumor mass involving the left stem bronchus. Both biopsy and cytology yielded a diagnosis of squamous cell carcinoma of the bronchus. Surgery was not feasible because of the patient's poor condition and death occurred October 24, 1951.

The next case reveals the fact that some cancers of the lung have a long history. The following patient's lung was resectable 38 months after photofluorographic abnormalities had been present but missed.

*Case 8:* J.G., a 61 year old white waiter, had a negative photofluorogram on March 14, 1947, and photofluorograms read negative December 31, 1947, January 7, 1949, and December 24, 1949. In retrospect, lesions at the right base were present in December, 1947, and January, 1949. The abnormalities were not obvious in the December, 1949, film. However, in February, 1951, the abnormality at the right base was finally noted. He was asymptomatic. A right middle lobe lobectomy on March 30, 1951, revealed adenocarcinoma. There was no lymph node metastasis. There has been no evidence of recurrence up to September 12, 1952.

The above patient was cooperative. There are, of course, individuals who simply refuse hospitalization due either to incredulity because of their sense of well-being, fear, or a fatalistic attitude. These problems constitute material for a whole study in themselves. However, there are, unfortunately, instances of delay on the part of physicians. The following is an example:

*Case 9:* J.L., a 43 year old white proprietor, had a negative photofluorogram on May 6, 1947 (Figure 7A). The photofluorogram of May 18, 1949 (Figure 7B), revealed a mass at the left base. Chest pain had been present in this area for two months. Five months after the presence of this mass was reported we were advised: "Lesion in the left lower lobe larger. In a reasonably short time, he will have an operation." On January 27, 1950, eight months after the abnormal photofluorogram, left pneumonectomy was done but metastasis to a mediastinal node was found. The man died one and one-half years post-operatively.

Just as it is impossible to prognosticate on the basis of a single film with proved tuberculous lesions, so one cannot tell the individual with an intrapulmonary mass how soon he will develop symptoms. The following case demonstrates the unpredictability of neoplastic growth and the fallability of even serial survey readings if photofluorograms are not compared with available previous films. In this instance, incredible as it may seem, the growing mass was only discovered four years after it was visible. The interpretation of areas of homogeneous ground glass density as "negative; thickened pleura" without comparing with previous available photofluorograms nullified the value of serial films.

*Case 10:* D.S., a 68 year old Negro waiter, had a "negative" photofluorogram in April, 1947 (Figure 8A). In retrospect there was a lesion at the right third anterior rib. The next year, 1948 (Figure 8B), he had a right infraclavicular mass but the radiological interpretation was "negative." Even less credible is the reading of "negative; thickened pleura" on the 1949 film in which the mass was larger. (When a photofluorogram is read "negative," no comparison is made with the previous films.) Again, in 1950, the photofluorogram was read "negative." Finally, in 1951, four years after the mass first appeared, the reader discovered it. At this time the waiter was 72 years old, and had fatigue and cough productive of yellowish, bloodstreaked sputum. Night sweats had been present for a short time. Hospitalization was refused. He continued to work. A photofluorogram taken eight months later, May 28, 1952 (Figure 8C), revealed volume shrinkage of the right upper lung. This man is still working and feels better than he did last year.

It is difficult for radiologists, trained as they are to make every effort at accurate diagnosis, to accept our survey policy of over-reading. Yet, only in this way will the survey screen develop a sufficiently fine mesh to yield maximal benefit.

The following case demonstrates the price one pays for ultra-conservative reading so far as tuberculosis is concerned:

*Case 11:* J.J., a 49 year old Negro kitchen man, was erroneously read "negative" September 20, 1948, instead of "suspect, right infraclavicular region." February 15, 1950, 17 months later, he had far advanced active disease. He died of tuberculosis six weeks later.

It is unfortunate that undue anxiety may be incurred in individuals suspected of having lesions subsequently found to be innocuous; such anxiety can be minimized by a properly indoctrinated follow-up team of nurses and doctors.<sup>4</sup>

Serial photofluorograms often provide the tuberculosis control officer with the tools necessary to convince the doubting patient of the need for hospitalization. The asymptomatic individual who cannot be convinced of his danger on the basis of a single film can almost always be convinced when shown two or more films which show definite progression.

### SUMMARY

Annual chest roentgenograms yield sufficient abnormalities to make them worth while. Like all survey films, they are only as good as their interpretations and subsequent follow-up. Serial film readings can be much more accurate than single film readings if the interpreters take the time to compare previously available photofluorograms. Serious errors can be compounded if readers are casual about classifying lesions.

Tuberculosis found following the existence of previously negative photofluorograms is of graver import than that found in routine first screening for prevalence. Therefore, there is urgent need of facilities for prompt care of these patients or their recently developed acute exudative lesions may progress rapidly to death despite the case-finding efforts. The advent of drug therapy makes it inexcusable to deny these patients treatment.

Serial films provide an opportunity to return to clinical supervision those who have strayed and whose new films reveal progressive disease.

Periodic chest x-ray films furnish a remarkable opportunity to study the natural course of untreated pulmonary disease. Diagnostic problems abound. Even with elaborate study, there always remain a few undiagnosed cases, some of whom regress under our photofluorographic eyes while others progress to a fatal termination.

### RESUMEN

Las radiografías de tórax hechas anualmente, proporcionan suficientes anomalías para que valga la pena hacerlas. Como todas las pesquisas en películas, ésta es tan buena de acuerdo con su eficiente interpretación y prosecución de los casos. Las series de películas, pueden ser mucho más exactas que la lectura de una sola película si los encargados de estudiarlas se toman el tiempo para comparar todos los fotofluorogramas obtenidos previamente. Se pueden cometer errores serios si los que interpretan las radiografías son informales sobre la clasificación de las lesiones.

La tuberculosis encontrada después de hallazgos previos negativos en radiografías anteriores, es de mayor importancia que la encontrada en las pesquisas radiográficas de rutina. Por tanto, es urgente el tratamiento in-

mediato de estos enfermos o de otra manera, sus lesiones agudas exudativas pueden evolucionar con rapidez hacia la muerte a pesar de los esfuerzos para descubrir los casos. El advenimiento de la terapéutica con las nuevas drogas, hace inexcusable el privar a estos enfermos del tratamiento.

Las películas en serie, proporcionan una oportunidad de volver a la revisión clínica de aquéllos que se han perdido de vista y cuyas nuevas películas revelan enfermedad evolutiva.

Las películas del tórax, periódicamente tomadas proporcionan un medio notable para estudiar la evolución natural de la enfermedad. Los problemas diagnósticos abundan. Aún con el estudio completo siempre quedan algunos pocos casos sin diagnóstico, algunos de los cuales retroceden en su evolución bajo nuestra inspección fotofluorográfica, en tanto que otros, marchan hacia un término fatal.

### RESUME

Les radiographies systématiques annuelles du thorax révèlent des anomalies suffisantes pour qu'on les tienne pour indispensables. Comme tous les examens, elles ne sont valables que par leur interprétation et l'examen complet qui lui fait suite. La lecture d'une série de radiographies est bien plus précise que la lecture d'un film unique à condition que les interprètes prennent bien soin de comparer les différents clichés. Des erreurs graves peuvent être faites si les interprètes ne classent pas rigoureusement les lésions.

La tuberculose découverte alors que les clichés antérieurs étaient normaux à une signification infiniment plus importante que celle découverte au premier examen systématique de contrôle. Pour ces malades, il est urgent de mettre en oeuvre avec énergie toutes les possibilités de traitement. Sinon les lésions découvertes récemment arrivent à progresser rapidement jusqu'à la mort. L'apparition de la chimiothérapie rend inexcusable toute négligence de traitement. Les examens systématiques donnent la possibilité de renvoyer à une surveillance clinique les cas douteux et ceux dont les nouveaux films révèlent une évolution.

Les examens en série fournissent une remarquable occasion d'étudier l'évolution naturelle de l'affection pulmonaire qui reste sans traitement. Les problèmes diagnostiques délicats sont nombreux. Même sérieusement étudiés, il reste toujours quelques cas qu'on ne peut diagnostiquer. Certains d'entre eux régressent spontanément, d'après les documents radiologiques, tandis que d'autres au contraire progressent jusqu'à la mort.

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# Pulmonary Postural Drainage for Bronchiectasis

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Although bronchiectasis is primarily a surgical disease, the patient beyond the help of surgery presents a major problem in its management and treatment. The purpose of this paper is to present simple forms of pulmonary drainage for bronchiectasis which may prove to be a valuable adjunct to accepted therapeutic measures.

A detailed study of methods of postural drainage has been made by the author and no simple method has been found in the literature that appears to be well tolerated by patients. Cecil, in his *Textbook of Medicine* states: "Postural drainage may be accomplished by hanging the head over the edge of the bed until it touches the floor, bending the body sharply over a chair, or markedly elevating the foot of the bed while using no pillows." These methods have been tried and found to be readily abandoned due to inability of the patient to tolerate them. Buckles, in *Surgical Treatment of Bronchiectasis* has used a tilting table and bed. The disadvantage in using the tilting table has been the need for an assistant as well as the inability of the patient to adequately persist in this type of drainage. The expense of this equipment must also be borne in mind. The special bed designed by Buckles helps gravitate secretions; however, it is not as practicable or applicable to every day use as one would desire.

In interviews with patients it was found that the usual method prescribed by physicians is lying over the edge of the bed in the morning with a member of the family helping to hold the patient in bed. This method has not met with success because it results in extreme dyspnea; also, it requires an assistant. The method of hanging over a chair also results in extreme dyspnea and fatigue and is impossible for some patients due to insecurity encountered in such a position.

It has been the experience of the author to find that the above methods, which appear to be most frequently recommended for bronchiectatic patients, are abandoned after a few attempts since they are exhausting, result in headaches, produce dyspnea, palpitation, flushing of the face and inadequate drainage of pulmonary secretions. Patients undergoing such exercises expend much effort in supporting themselves and not concentrating on ridding themselves of the pulmonary secretions. Elderly patients in particular, who are chronic bronchiectatics, find it difficult to assume and continue in these types of pulmonary drainage.

The bronchiectatic patients treated by postural drainage in this series are those who have been found to have moderate to extensive disease, usually on both sides, who are not surgical candidates. These patients may be treated by antibiotic therapy and all other helpful measures, bearing in mind pulmonary postural drainage being of the greatest aid in evacuating the bronchiectatic cavities. It is apparent that these patients will follow



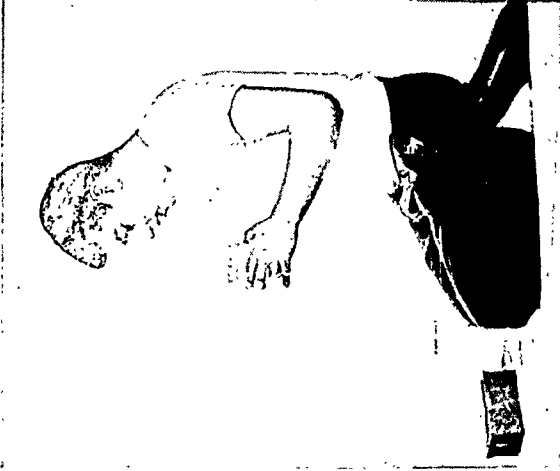


FIGURE 1A



FIGURE 1B



FIGURE 1C

*Figure 1A: Starting position—resting on heels.  
Figure 1B: Knee-chest position.  
Figure 1C: Resting position.*

the advice of a physician who prescribes the most simplified methods of pulmonary postural drainage.

Five years ago the author was afflicted with bronchial asthma. In an effort to eliminate tenacious bronchial mucous plugs at night, it was his experience to note that by lying with three pillows placed underneath the abdomen in a knee-chest position, alternating intermittently in a sitting position in order not to become dyspneic, that adequate pulmonary drainage was easily tolerated. The importance of alternating the knee-chest position and the sitting position cannot be too highly stressed for it was found to be an integral part of the successful accomplishment of the pulmonary drainage since it was efficacious in not causing dyspnea or fatigue. Further studies were done to find simplified and practicable methods for pulmonary drainage and were applied. The results have been most gratifying as attested to by many patients in a period of five years. Four simple methods of pulmonary postural drainage have been utilized in this study.

The best method found by the author has been the knee-chest position. Immediately upon arising, before breakfast, patient is instructed to undergo drainage in this position. It has been found that some patients prefer to move around after arising before undergoing drainage for it has been their experience that "loosening" of the sputum occurs in so doing. A flat surface is to be preferred. A bed is not suitable unless the mattress and spring are very firm and result in no sagging with body weight.

In the knee-chest position, the patient assumes starting position as in Figure 1A, being erect, resting on his heels. This position is then followed by assuming the knee-chest position lying on the forearms with palms outstretched as in Figure 1B. The knee-chest position permits the head and shoulders well below the body of the pelvis and at this stage it is important to pay attention to the thighs being perpendicular to the flat surface of the floor for this permits a greater degree of gravitational drainage of secretions and evacuation of bronchiectatic cavities. As the patient is lying in position, he undergoes several expulsive coughs, expectorating secretions in a disposable paper container.

The importance of the cough being a protective reflex should be explained to the patient at this stage and he should be instructed to breathe in, breathe out, and then cough at the end of expiration similar to the coughing that the physician requires in eliciting post-tussive crepitant rales. The bechic blast with the cough is helpful in eliminating the secretions that lie in the upper tracheobronchial tree. The patient should be instructed to remain only a few minutes in the knee-chest position and immediately thereafter resume resting position as in Figure 1C. The reason for remaining in the knee-chest position only a few minutes is because it has been the author's experience that the patient becomes fatigued, short of breath, face flushes, and as soon as this occurs becomes discouraged and gives up the exercises. If, however, he remains in the knee-chest position for a few minutes and is able to assume resting position as in Figure 1C, he will regain his strength by resting and thus repeat the knee-chest position until such time as he is able to eliminate all secretions.

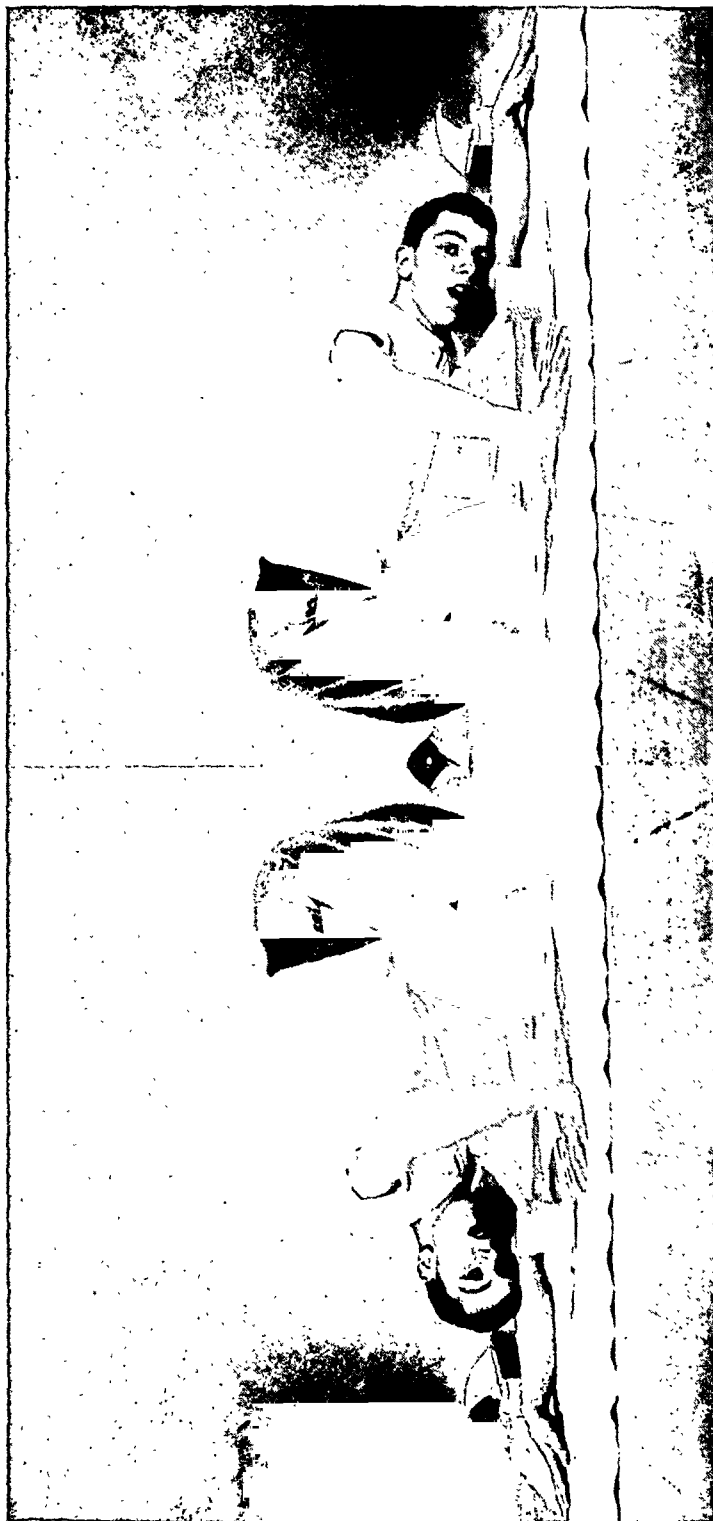


FIGURE 2A

*Figure 2A: Left lung drainage.*

*Figure 2B: Right lung drainage.*

FIGURE 2B

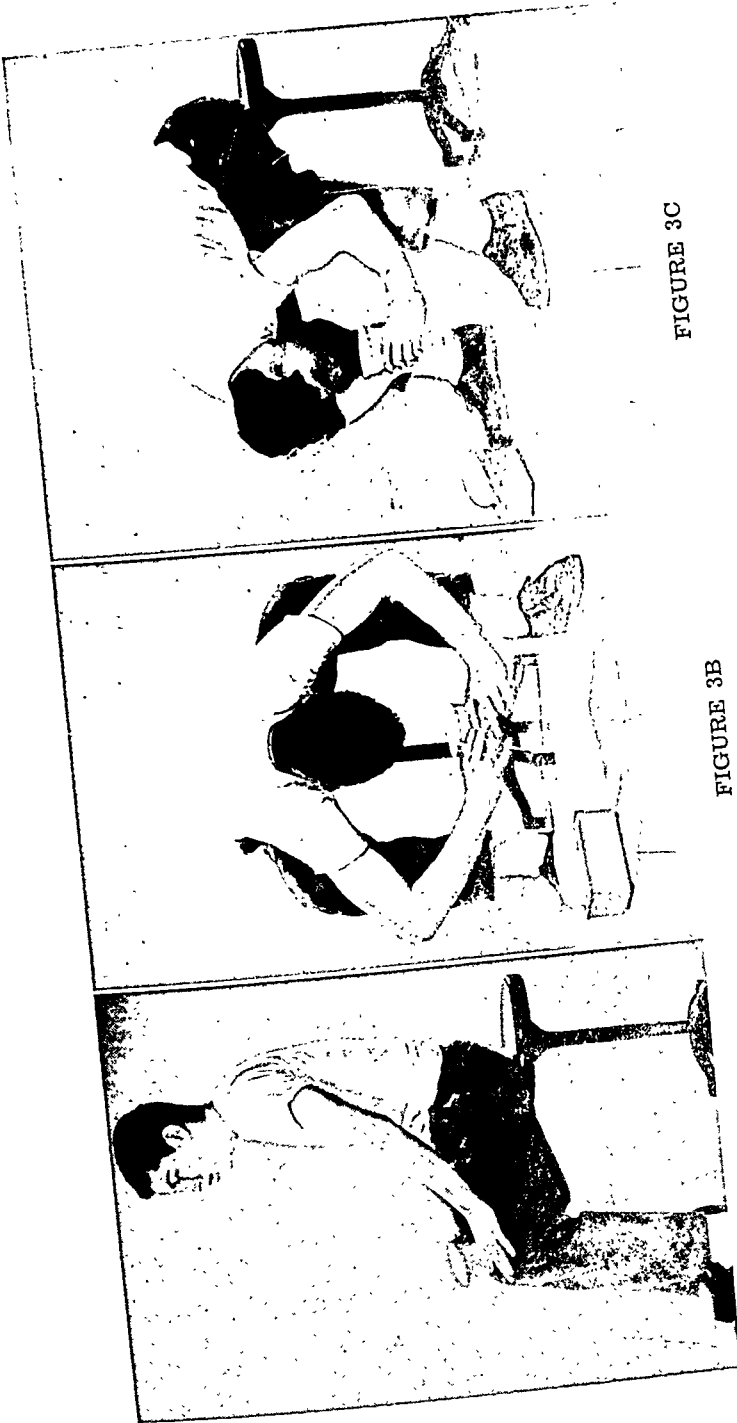


FIGURE 3A

Figure 3A: Starting position.

FIGURE 3B

Figure 3B: Elbow-to-knee drainage position, side view.

FIGURE 3C

Figure 3C: Elbow-to-knee drainage position, front view.



FIGURE 4A



FIGURE 4B



FIGURE 4C

*Figure 4A: Elbow-to-knee, side view — no chair.*  
*Figure 4B: Elbow-to-knee, front view — no chair.*  
*Figure 4C: Drainage of left lung.*

# POSTURAL DRAINAGE FOR BRONCHIECTASIS



FIGURE 5A

Figure 4D: Drainage of right lung.  
Figure 5A: Crouching position.



FIGURE 4D

In an effort to promote more complete drainage of each lung, the patient may partially rotate his trunk in the knee-chest position as in Figures 2A and 2B, lying on the right and left sides respectively. In this position the head rests on the arm and forearm of contralateral lung being drained and the opposite arm is used to help balance the body and rotate it so that the lung being drained is slightly higher permitting secretions to gravitate.

It is noted in literature on bronchiectasis that patients are advised to undergo the strenuous positions described earlier for a half hour several times a day. In the author's experience, each one must be treated as an individual case. Those undergoing knee-chest pulmonary postural drainage exercises are advised to note the quantity and consistency of the sputum daily to see for themselves the gradual reduction in the quantity and change in character from purulent to less purulent and mucoid consistency after a period of days. In pursuing this schedule of exercise for pulmonary toilet, patients are in a better position than the physician to note the amount of time that is required to drain pulmonary secretions. Early in the procedure 15 to 20 minutes may be required, whereas after the exercise has been productive of results only three to five minutes may be necessary. The elimination and reduction of cough and expectoration encourages many persons to adhere to this method of knee-chest position of cleansing the pulmonary tree. The need to be socially acceptable and being enabled to remain on the job is a source of happiness and economic security to many patients. Good drainage also aids appreciably in removal of bad breath when the cause is due to retained pulmonary secretions from bronchiectasis.

Bronchiectatic patients are educated to the fact that daily undergoing of knee-chest exercises for pulmonary postural drainage is a must such as the brushing of the teeth. The physician in charge must pay close attention to details, such as the exact position of the patient and the time he allots to the exercises. Inasmuch as the time interval obviously depends on the degree of bronchiectasis, it has been the experience of some persons to find it unnecessary to continue the exercises every day of the week because of the adequate pulmonary drainage encountered in this method. A group of patients take the exercises only during the days that they feel retained secretions are present and pursue them until such time as all secretions are eliminated and, therefore, undergo intermittent postural drainage alternating with rest periods for a few days. It has been pointed out to these patients that the rest periods must not be too prolonged since they may result in inadequate pulmonary drainage.

Experience has also shown that it is necessary to undergo the exercises throughout the day, depending on the amount of sputum. Patients are required to do the exercises before or between meals and not after eating. The one who diligently undergoes good morning drainage is usually able to go until before the noon meal. The patient who complains of cough and expectoration upon retiring and who states he cannot fall asleep unless he coughs himself to sleep has found distinct benefit in doing the knee-chest pulmonary postural drainage exercises before retiring.

Although the knee-chest exercise has been found to be the best method, daily activities are not always conducive to applying it. For these patients the author has supplemented the elbow-to-knee position. Although it is not as effective as the knee-chest position, it is a very simple method for observation has shown that on occasion persons assume the position without being cognizant of it. In the elbow-to-knee position the patient sits on the end of a chair as in Figure 3A (normal sitting position will not permit flexing of the body forward). With knees flexed, legs apart slightly more than the width of the shoulders, feet firm on the floor, legs perpendicular to the floor, trunk flexed as far downward as possible, patient places elbows in front of knees as in Figure 3B. He then undergoes expulsive cough and bechic blast. Again, the importance of resting, as in knee-chest position, cannot be over-emphasized.

The elbow-to-knee position was found to be more efficient without the aid of a chair for it permits a greater degree of gravity and can be carried out at any time or place. Experience has shown that it requires little practice. Without the chair, elbows rest on the knees; whereas with the chair, elbows are placed in front of the knees. While in this position, the trunk is flexed as far downward as possible as in Figures 4A and 4B and patient undergoes expulsive cough exercises. Again, the importance of rest in an erect posture is stressed. Another advantage without the chair is that it enables drainage of each lung by rotating the trunk downward which is difficult with a chair. It is important to note as in Figures 4C and 4D that one shoulder is lower than the other, elbow of the contralateral lung lies inside the knee and opposite hand rests on knee for support.

For those unable to undergo either the knee-chest or elbow-to-knee positions because of arthritis, deformities of the pelvis or age, the author has devised the crouching position which is done by resting with one forearm and hand on a chair while opposite arm helps support the body on another chair, and bending as far forward as possible by flexing the trunk as in Figure 5A. While in this position, patient undergoes expulsive cough exercises. Periods of rest in these cases, sitting or lying, are important.

Difficulties encountered in these exercises usually arise from misunderstanding and may result in loss of interest with failure to obtain desired results. Repetition of exercises under supervision of physician and re-education promote success. Routinely, the author demonstrates to the patient graphically what occurs in bronchiectasis and during postural drainage. Viewing x-ray films in order to visualize the location of disease enables patient to appreciate the importance of gravity for drainage of secretions. Photographs in this study of a person in postural drainage positions have also been found helpful as a teaching method.

### SUMMARY

Four simple methods of pulmonary postural drainage for bronchiectasis have been outlined.

The knee-chest position has been found to be the most successful for it removes a large portion of secretions whenever used.



The elbow-to-knee position with and without the aid of a chair, being simple, supplements the knee-chest for it can be used at any time or place.

The crouching position has been helpful in arthritic and elderly patients.

Experience has proved over a period of five years that patients become expert in the procedure for they are well tolerated, do not require props, assistance or expense.

Helpful aids in individual education are outlined.

These four exercises have been found to be practicable for bronchiectasis as well as other pulmonary diseases requiring drainage, such as tuberculous basal cavities, purulent tracheobronchitis, lung abscess in the lower lobes, bronchial asthma (depending on the severity of dyspnea), asthma complicated by bronchiectasis and pulmonary emphysema. The exercises are also helpful before bronchographic study and surgical procedures requiring pulmonary drainage.

### RESUMEN

Se han descrito cuatro métodos sencillos de drenaje postural para la bronquiectasia.

La posición genupectoral, se ha encontrado ser la más efectiva, porque permite expeler gran parte de las secreciones siempre que se usa.

La posición de codos en las rodillas con y sin la ayuda de una silla siendo sencilla, suple a la genupectoral, puesto que puede usarse en cualquier tiempo y lugar.

La posición agachado, es útil en los ancianos y en los artríticos.

La experiencia por más de cinco años, ha demostrado que los enfermos se hacen expertos en los procedimientos porque son bien tolerados, no requieren adminículos, ayuda o gastos.

Se señalan algunas cosas auxiliares en la educación individual.

Se ha encontrado que estos cuatro ejercicios, son practicables para bronquiectasia, así como para otras enfermedades que requieren canalización bronquial, tales como la tuberculosis de las bases, traqueobronquitis purulenta, abscesos de los lóbulos inferiores, asma bronquial (dependiendo de la severidad de la disnea), asma complicada con bronquiectasia y enfisema pulmonar. Los ejercicios son tan bien una buena ayuda antes del estudio broncográfico y de procedimientos quirúrgicos que requieren canalización de secreciones pulmonares.

### RESUME

L'auteur insiste sur quatre méthodes très simples de drainage de posture dans les cas de dilatations des bronches. La plus satisfaisante lui a semblé être la position genupectorale, car chaque fois qu'elle a été utilisée, elle a permis l'évacuation d'une grande quantité de sécrétions.

La position coude aux genoux, avec ou sans l'aide d'une chaise est un simple complément de la position genupectorale car elle peut être utilisée n'importe quand et n'importe où.

La position accroupie a été très utile chez les malades arthritiques ou âgés.

L'expérience à montré, à la suite de cinq années d'essais que les malades eux-mêmes acquièrent une grosse expérience dans les procédés qu'ils supportent bien, et qu'ils n'ont besoin d'aucune assistance particulière.

L'auteur insiste sur l'aide efficace que comporte l'éducation de chaque malade.

Ces exercices ont semblé utilisables aussi bien pour les dilatations des bronches que pour les autres affections pulmonaires nécessitant un drainage (cavernes tuberculeuses de la base, trachéo-bronchites purulentes, abcès du lobe inférieur, asthme bronchique avec dyspnée importante, asthme compliqué de dilatation des bronches, emphysème pulmonaire). Ces exercices sont également d'un grand intérêt avant bronchographie, et avant les actes chirurgicaux nécessitant un drainage pulmonaire.

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# Obstruction of the Esophagus by Diseased Ectopic Gastric Mucosa\*

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In the past decade, advances in anesthesiology, antibiotics, pre- and post-operative care and surgical technique have greatly increased the scope of thoracic surgery. Among those profiting by these advances, is the individual suffering from esophageal obstruction.

Recently reported benign lesions producing esophageal obstruction include acylasia, chemical obstruction, congenital obstruction, webs, congenital strictures, perforation (spontaneous and traumatic) and fistulae. It is our purpose to present two cases of esophageal obstruction due to diseased ectopic gastric mucosa and to emphasize the desirability of carefully evaluating the cause of obstructive lesions in order to remove the possibility of overlooking a non-malignant lesion. Inasmuch as diagnosis of such lesions today is often based upon direct visualization by esophagoscopy and by barium studies, it is possible to believe that some so-called malignancies of the esophagus are in truth quite benign and amenable to surgical correction. It has been the experience of many thoracic surgeons and pathologists that repeated attempts at biopsy of such lesions have failed to prove the presence of a cancer. In such instances, the clinical diagnosis of carcinoma, although unsupported, often prevails and is accompanied by unjustified pessimism. On the basis of the following two cases it is believed that a more detailed study of possible benign lesions of the esophagus is mandatory.

Ectopic gastric mucosa is not an infrequent finding. It has been reported in the upper third of the esophagus,<sup>14,17</sup> the lower third of the esophagus,<sup>10,14,18</sup> within gastric cysts of the mediastinum,<sup>3,4,13,16</sup> chronically inflamed gall bladders, cysts of the pancreas, Meckel's diverticula<sup>1,2,5,6,8,9,11,15,17</sup> chronic tuberculous ulcers of the colon<sup>6</sup> and in teratomas. These islands of gastric mucosa, no matter where they may occur, are subject to all the diseases and malformations to which gastric mucosa is heir. These include acute and chronic inflammations, ulcerations, polypoid hyperplasias, and hypertrophies. When symptoms arise from such ectopic foci, they usually are due to ulceration of the focus with subsequent hemorrhage and/or pain. In each of the cases presented here, however, the primary symptom was esophageal obstruction which later proved to be caused by ectopic foci of gastric mucosa which had become diseased.

*Case 1:* A 45 year old white female entered the hospital because of vomiting and dysphagia which had its onset six months prior to admission and was

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accompanied by a sensation of food lodging in the lower esophagus. This condition became progressively worse until two weeks prior to admission, at which time two attempts at esophageal dilatation were made. These afforded some relief but on the day prior to admission she became much worse, was nauseated, vomited and could retain only fluids.

History and physical examination were essentially negative. She showed no evidence of weight loss. Routine laboratory studies were normal. Esophagograms showed a sharply outlined obstruction at the junction of the middle and lower thirds of the esophagus (Figure 1). On November 1, 1951 esophagoscopy was performed and an obstructing lesion was seen 30 cm. from the gum margin. A biopsy was obtained and bougies were passed in an attempt to dilate the obstruction. The pathologic diagnosis of the biopsy specimen was esophagitis ulcerative, severe. The inflammatory reaction was so severe that the tissue pattern was destroyed and much of the specimen consisted merely of fibrino-purulent exudate. No specific epithelium was identifiable.

The pathologist in his report made a supplementary comment that from the

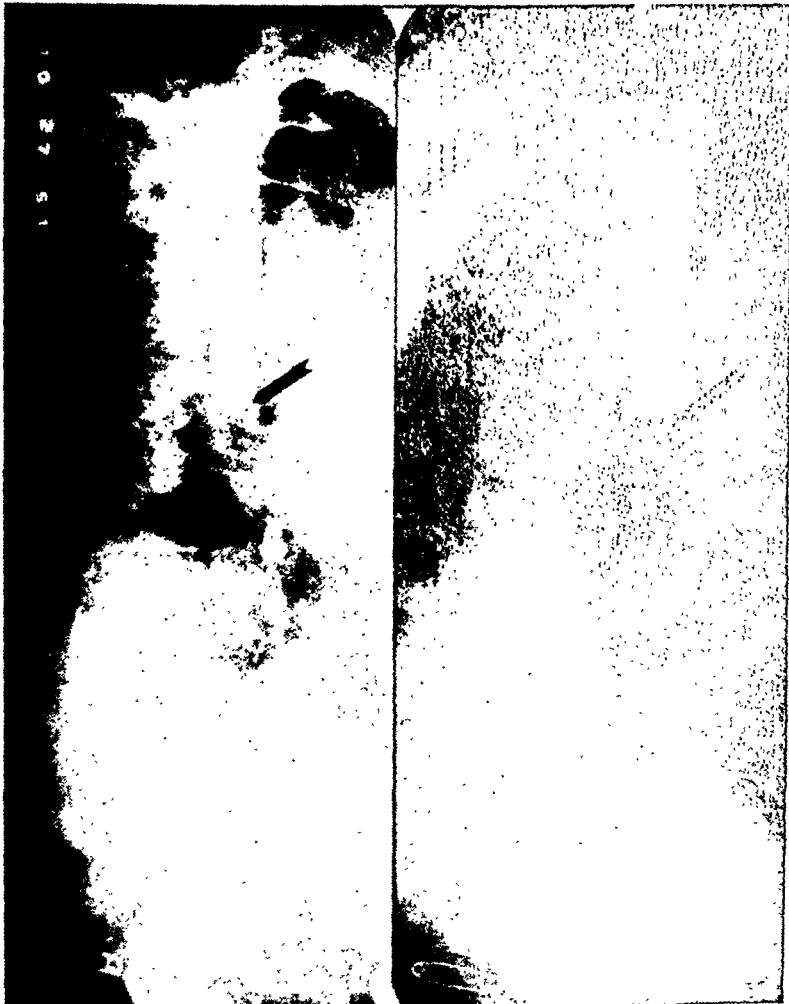


FIGURE 1 (Case 1): Esophagograms demonstrating an esophageal obstruction at the junction of the middle and lower thirds of the esophagus.

microscopic appearance the lesion might possibly be ectopic nests of gastric mucosa. On November 6, 1951 the endoscopic examination was repeated, and a second biopsy was obtained (Figure 2). This was reported as, "1. Gastric mucosa, ectopic, polypoid, of the esophagus. 2. Esophagitis, chronic, ulcerative, severe. 3. Esophagitis acute, focal, severe."

With each of the endoscopies, attempts had been made to dilate the esophagus, but these had not been successful. An exploratory thoracotomy was advised.

On December 7, 1951 with the patient in the conventional left lateral position, the thorax was opened. After the rib spreader had been placed, the pulmonary ligament was dissected up to the level of the inferior pulmonary vein. The mediastinal pleura was then opened and the esophagus mobilized. The wall of the lower 8 cm. of the esophagus was found to be markedly thickened and adherent to the surrounding structures. After freeing up the involved area, the esophagus was incised in a longitudinal direction. The lumen was completely obstructed. A biopsy of the entire thickness of the wall was taken, and submitted for frozen section. The report on the biopsy was as follows, "Esophagitis chronic and acute, ulcerative, severe. Hyperplasia polypoid, adenomatous, of ectopic gastric mucosa within the esophagus." The diaphragm was then opened, and the lower segment of the esophagus was resected. Examination disclosed characteristic gastric mucosa (Figure 3). An anastomosis between the fundus and the esophagus was carried out without difficulty. Further details of the operation technique have been omitted because they have become standardized. Her post-operative course was uneventful.

*Case 2:* A 54 year old white female experienced difficulty in swallowing for six months. This had its onset one month following cholecystectomy. The dysphagia consisted of an uncomfortable low substernal sensation on swallowing solid food. This was relieved by liquids. These symptoms persisted and progressed to the point where only liquids could be taken. There had been a 30 pound weight loss, during this period. Routine laboratory studies were essentially negative. Esophagograms revealed an obstructing lesion of the esophagus in the lower third (Figure 4).

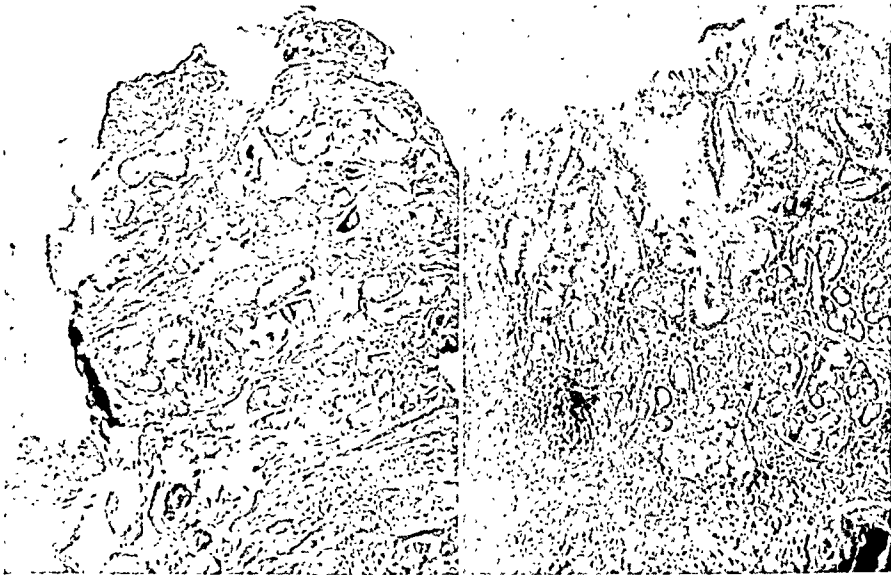


FIGURE 2

FIGURE 3

*Figure 2 (Case 1):* Photomicrograph (x 100) taken of second esophageal biopsy, showing typical gastric mucosa with adjacent nest of squamous epithelium.—  
*Figure 3 (Case 1):* Photomicrograph (x 100) taken of resected segment of esophagus.



FIGURE 4 (Case 2): Esophagogram showing persistent filling and obstruction of the lower third of the esophagus.



FIGURE 5 (Case 2): Gross specimen. Resected portion of esophagus showing polypoid, hemorrhagic gastric mucosa.



FIGURE 6

FIGURE 7

FIGURE 8

Figure 6 (Case 2) : Photomicrograph (x 50) of esophageal biopsy. In this instance the entire tissue is partially autolysed and disintegrating. Outlines of tubular structures can be seen but the character of their composition is uncertain and this, no doubt, accounts for the erroneous diagnosis of hemangioma. — Figure 7 (Case 2) : Esophagus at time of operation. Esophagus has been opened, exposing the hemorrhagic polypoid structure which obstructed the lumen.—Figure 8 Case 2) : Photomicrograph (x 50) showing transition from normal esophageal epithelium to ectopic polypoid gastric mucosa.

There was no evidence of congenitally short esophagus or hiatal hernia in either case.

On November 9, 1951 diagnostic esophagoscopy was carried out. There were accumulated secretions all the way down. After aspirating the secretions, a brief view was obtained of what appeared to be a tumor mass, but contact of this area with the suction tip produced severe bleeding. The bleeding continued and the lesion could not be revisualized. On November 13, 1951 esophagoscopy was repeated and this time the lesion was well visualized. It had the appearance of a very injected polyp (Figure 5). Biopsy was obtained which was reported as follows, "Hemangioma of the esophagus" (Figure 6). An exploratory thoracotomy was advised.

She was prepared in the usual fashion and on December 6, 1951 thoracotomy was performed as described in the previous case. After mobilizing the esophagus, an area similar in length to that of the previous case was encountered. Again the esophagus was opened longitudinally and complete obstruction was present (Figure 7). Biopsy and frozen section revealed "ectopic gastric mucosa." This was subsequently confirmed on the permanent section (Figure 8). Resection and anastomosis was carried out as in the previous case (Figure 5). The immediate post-operative course was uneventful. Eight weeks post-operatively she had difficulty swallowing solid foods. She was again esophagoscoped. The site of the anastomosis appeared normal but somewhat narrowed. This was easily dilated. Subsequent dilatation was required on one other occasion.

Both cases are now doing well.

### Discussion

In the first case, the lesion covered a large area showing peptic ulceration, cicatrization, and stenosis. In some places gastric mucosa was preserved but in other areas the ulceration had completely destroyed the usual mucosal structures. This process can be so extensive as to obliterate completely all semblance of the gastric mucosa. By virtue of the histopathologic processes, however, it is possible in many instances to consider ectopic gastric mucosa as an underlying factor in so-called widespread ulcerative necrotizing esophagitis. Recently we have had a third case which was initially thought to be due to gastric mucosa. However, following resection of the stenosed area, it was found that the ulceration involved the entire surface and that it was no longer possible to identify the epithelial structures.

In the second case, the obstruction was due to polypoid hyperplasia of gastric mucosa. It is, by analogy, reasonable to suppose that within such islands of gastric mucosa, changes could occur similar to those within the stomach or Meckel's diverticula. The mechanical obstructing component of the disease in the esophagus, however, is far more important than in either of the lower locations.

Inasmuch as these lesions will mimic malignancy by virtue of their clinical signs of obstruction, weight loss, pain, bleeding, and x-ray patterns, we feel that the surgeon should possess conclusive proof of the essential malignancy of the lesion before he admits defeat. In the absence of positive histologic evidence of cancer, repeated attempts to establish a precise diagnosis should be made. If, after reasonable attempts, a diagnosis has not been established, the patient should be given the benefit of an exploratory thoracotomy.



## SUMMARY

1) Two cases of esophageal obstruction due to diseased ectopic gastric mucosa are reported.

2) On the basis of these and similar cases, it is urged that the obstructive lesions of the esophagus should never be classified as malignant on a basis of clinical, roentgen, and endoscopic appearances alone. If definite histologic proof is not otherwise available, the patient should receive the benefit of surgical exploration.

## RESUMEN

1) Se refieren dos casos de obstrucción del esófago debida a mucosa gástrica ectópica.

2) Sobre la base de estos y de casos similares es preciso que las lesiones obstructivas del esófago no sean clasificadas como malignas apoyándose en las apariencias clínica, radiológica y endoscópicas solamente. Si no se obtiene una prueba histológica concluyente el enfermo debe beneficiarse de una exploración quirúrgica.

## RESUME

1) L'auteur rapporte deux cas d'obstruction oesophagienne dus à une ectopie pathologique de la muqueuse gastrique.

2) En se basant sur ces deux cas, et sur d'autres similaires, il est de première importance de savoir que le diagnostic de cancer ne doit pas être fait en présence d'obstruction oesophagienne, sur les seuls caractères clinique, radiologique ou endoscopique. Si par ailleurs, la preuve histologique ne peut être apportée d'une façon valable, il ne faut pas hésiter à faire bénéficier le malade de la chirurgie exploratrice.

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# Clinical Differentiation of Pulmonary Infarction

(Correlation of Clinical and Pathologic Findings)

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On the medical service of a neuropsychiatric hospital the clinical diagnosis of acute pulmonary infarction can be especially difficult. Most psychotic patients cannot relate good histories. Evaluation of symptoms and of signs is fraught with obstacles. The classical syndrome of chest pain, hemoptysis, consolidation of lungs, friction rub, and shock may not be present. The laboratory studies are at times of questionable value; the electrocardiogram may be misleading, particularly if it is used as the sole differentiating criterion; and the x-ray studies too may be confusing.<sup>1</sup> The problem is further complicated because this lesion may coexist with or follow pneumonia or other serious illness. In order to determine the factors which might aid in the clinical diagnosis of pulmonary infarction, we have reviewed the pathological material at this hospital during the five year period January 1, 1947 to December 31, 1951; and correlated it with the clinical findings.

In that period there were 391 deaths and post-mortem examinations were performed in 255 instances. In 19 cases, there was pathologic evidence of pulmonary tissue necrosis with either pulmonary arterial embolism, pulmonary arterial thrombosis, or both; in short, there were 19 male patients with pulmonary infarction. This incidence of 7.4 per cent is in agreement with figures of Katz<sup>2</sup> et al and of Belt, cited by Katz.

Eighteen of the patients were white and one was a negro. No statistical significance is attached to this finding because the majority of post-mortems were on white people.

Table I lists the psychiatric diagnoses established for 13 of our patients prior to death. There were also six without psychiatric diagnoses.

In our series the age distribution is shown in Table II. The majority (58 per cent) were in the 51 to 60 age group.

Two of the 19 infarctions developed post-operatively: one, nine days post-cholecystectomy (after leaving bed the first time); the other, 21 days after gastric resection (in a patient still confined to bed). One suffered

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From the Medical Service of the United States Veterans Administration Hospital, Lyons, New Jersey; published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

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TABLE I

Schizophrenia .....	4
Psychosis with arteriosclerosis .....	2
Psychosis with central nervous system, syphilis .....	1
Psychosis with arteriosclerosis and central nervous system, syphilis .....	1
Psychosis with alcoholism .....	1
Psychosis with grand mal epilepsy .....	1
Psychosis with multiple sclerosis .....	1
Manic depressive psychosis .....	1
Psychopath .....	1

TABLE II

41-50 .....	1	
51-60 .....	11	(58 per cent)
61-70 .....	5	
71-80 .....	2	

from aplastic anemia, which was confirmed by repeated bone marrow studies for a year, before developing infarction. One was thought to succumb to a cerebral thrombosis. Three were considered to have terminal pneumonia, one of whom was believed to have colon carcinoma with pulmonary metastases in addition to the pneumonia.

The remaining 12 had clinical evidence of heart disease. One had rheumatic heart disease; three hypertensive cardiovascular disease; and eight had arteriosclerotic heart disease. The detailed cardiac diagnoses are listed in Table III.

TABLE III

Rheumatic heart disease with bacterial endocarditis
Hypertensive cardiovascular disease
Hypertensive cardiovascular disease and pulmonary tuberculosis
Hypertensive renal disease with cardiac failure
Arteriosclerotic heart disease; acute myocardial infarction
Arteriosclerotic heart disease; cardiac failure (two cases)
Arteriosclerotic heart disease; cardiac failure, pneumonia
Arteriosclerotic heart disease; cardiac failure, saddle aortic embolus
Arteriosclerotic heart disease; pneumonia
Arteriosclerotic heart disease; pneumonia, pulmonary tuberculosis
Arteriosclerotic heart disease; pneumonia, decubitus ulcers

One patient developed pulmonary infarction shortly after leaving bed for the first time on the ninth day after operation. The other 18 *had been in bed* for many days prior to the onset of pulmonary infarction.

Eleven expired within 24 hours of the onset of the terminal syndrome; three in shock and eight in coma. The remaining eight lived longer than 24 hours, and as might be expected from the duration of their illness, seven became comatose while only one died in shock.

Pneumonia was diagnosed ante mortem in seven cases but was confirmed post-mortem in only three. Heart disease was diagnosed ante mortem in

12 cases but was confirmed post-mortem in only 10. However, six additional unsuspected cases of heart disease were found at autopsy. Thus, there were 16 of the 19 with heart disease antedating pulmonary infarction. The types of heart disease found at post-mortem are listed in Table IV.

TABLE IV

Arteriosclerotic heart disease.....	13
Rheumatic heart disease ..	4
Congenital .....	1
Cor pulmonale (secondary) .....	1

Nine patients exhibited thrombo-embolic phenomena at sites other than the lungs. The sites and relative frequency are listed in Table V. The table reveals that four had intracardiac mural thrombi, three had prostatic venous thrombosis; and one had inferior vena cava thrombosis.

TABLE V

Intracardiac mural ...	4
Prostatic venous plexus .....	3
Aorta .....	2
Spleen .....	2
Femoral artery .....	1
Iliac artery .....	1
Mesenteric artery .....	1
Inferior vena cava.....	1
Liver .....	1

Five had neoplastic disease; of these, two were diagnosed ante-mortem\* and three at time of necropsy. They are listed in Table VI.

TABLE VI

*Carcinoma of tongue.....	1
*Carcinoma colon of colon with metastases to lungs.....	1
Carcinoma of colon.....	1
Carcinoma of pancreas .....	1
Meningioma .....	1

### Discussion

There is an idea prevalent in the literature and exemplified by White<sup>3</sup> that psychotic individuals, particularly schizophrenics, rarely have heart disease. Unpublished data from this hospital<sup>4</sup> indicate that schizophrenics suffer from heart disease at least as frequently as do the general population. Our data indicates that during the period considered there were 133 post-mortem examinations on psychiatric patients. The diagnosis was schizophrenia in 36 per cent. Table I indicates that there were four schizophrenics who developed pulmonary infarctions. We should like to emphasize that pulmonary infarction is not rare in schizophrenics.

In 1947-48, one of us<sup>1</sup> studied 1,172 psychotic patients in this hospital; those in the age group 51 to 60 numbered 666 (57 per cent). Our data (Table II) indicates that 58 per cent of the infarctions occurred in this same age group. Age per se does not appear to be an etiologic factor in pulmonary infarction since the proportion in the 51 to 60 range was found to be similar in the hospital population and in the present study (vide supra).

Although pneumonia was diagnosed ante-mortem in seven cases it was confirmed only in three. Since the clinical and laboratory findings are often similar, the two conditions are frequently confused. When an elderly patient confined to bed develops the clinical picture of pneumonia, it is necessary to exclude pulmonary infarction.

During the period, considered the gross autopsy incidence of heart disease at the hospital, among the psychotic patients, was 71 per cent.<sup>4</sup> In our group with pulmonary infarction, the gross autopsy incidence of heart disease was 84 per cent. This is considerably greater than the 30 per cent implied by Katz and Walsh in citing data of Hampton and Castleman.<sup>2</sup>

Disease of the heart itself may not play a role in the causation of pulmonary infarction but we feel, as do Musser<sup>5</sup> and Moran<sup>8</sup> that cardiovascular disease in general predisposes to thrombo-embolic phenomena. This may be particularly so with regard to atherosclerosis. It may be a coincidence but in our 19 cases with pulmonary infarction not one evidenced stigmata of syphilitic cardiovascular disease at autopsy, yet during this same period 19 per cent<sup>4</sup> of those with heart disease evidenced at post-mortem had lesions of syphilitic cardiovascular disease. This absence of syphilitic cardiovascular disease in our group may be related to pathogenesis. In syphilis the tunica media is involved, particularly in the proximal ascending aorta; while in atherosclerosis the intima is more involved. Perhaps the intimal lesions predispose more to thrombus formation, than do primary medial lesions.

In our 19 patients 18 had been in bed many days before the onset of pulmonary infarction and one developed infarction shortly after leaving bed the first time in nine days. Immobilization in the supine position is a predisposing factor. This is in agreement with current thought.<sup>6</sup>

Neoplasms were found in five (26 per cent) patients with pulmonary infarction, but in only 16 per cent of all the autopsies on psychotic patients done during the same period.<sup>2</sup> Although this is a small series; it may be that neoplastic disease predisposes to thrombo-embolic disorders.

#### SUMMARY

- 1) Nineteen patients with pathologic evidence of pulmonary infarction were studied in a neuropsychiatric hospital.
- 2) Clinical and pathologic diagnoses were correlated.
- 3) The occurrence of pulmonary infarction in psychotic individuals is not uncommon.
- 4) Certain predisposing factors were elicited.
- 5) Pulmonary infarction and pneumonia are often confused clinically.

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# The Reversibility of Pulmonary Overdistention

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The problems of treatment posed by total pneumonectomy have always been two-fold. First, the creation of a large dead space was contrary to a cardinal principle of surgery. Secondly, the fate of the "good lung" from both the physiological and pathological standpoint, has been the subject of conjecture.

The problem of a large dead space appeared frightening to Graham<sup>1</sup> when he performed his first pneumonectomy. He solved this problem by performing a concomitant thoracoplasty to obliterate it. By so doing, he doubtlessly minimized overdistention of the remaining lung and thus solved the second problem in a satisfactory manner.

Gaensler and Strieder<sup>2</sup> have shown that early thoracoplasty appears more valuable than late thoracoplasty from a function-sparing standpoint but indicate that thoracoplasty per se, even over a dead space, results in some functional loss. Nevertheless, Strieder<sup>3</sup> believes that post pneumonectomy thoracoplasty is a worth-while procedure, if only to prevent annoying cough and make the patient more comfortable.

It is generally agreed upon that prevention of overdistention is desirable. This is so, especially, since the results of treatment, when overdistention has become clinically established, are not satisfactory.

Furthermore, no standardized method of correction of overdistention has been evolved. Various authors have advocated thoracoplasty, pneumothorax, oleothorax, and procedures employing plombage in an effort to allow the mediastinum to stabilize in its normal position in the midline. On the other hand there are surgeons who do not employ post-pneumonectomy space obliterating procedures to preserve function. They believe overdistention is only dangerous in the tuberculous patient where it may result in breakdown of foci in the opposite lung.

It was surprising to us to find<sup>4,5</sup> that few statistics were available to document the clinical improvement often seen following treatment for well established postsurgical compensatory emphysema. The following case histories are presented to substantiate the authors' impression that the often striking amelioration of symptoms following treatment of pulmonary overdistention must have some basis in fact.

*Case 1:* A 54 year old white male who had undergone right pneumonectomy for bronchogenic carcinoma two years prior to the time he was first seen by us. The operating surgeon had not performed a thoracoplasty because he believed he had not achieved a cure and felt that the patient would not experience incapacitating ventilatory difficulties within his predicted life expectancy. The patient was hospitalized because of extreme shortness of breath on mild exercise. His maximum breathing capacity was 19 liters per minute; his walking ventilation was 16 liters per minute. The mediastinum was retracted entirely within the right chest and there was a severe overdistention of the remaining left lung. Pneumoperitoneum was instituted; the initial amount of air was 2,000 cc's. He received refills at four



day intervals thereafter for two weeks. He experienced marked symptomatic relief of dyspnea and at the end of this time his maximum breathing capacity was 44 liters per minute and his walking ventilation was 15 liters per minute. The patient did not tolerate pneumoperitoneum well and had much abdominal discomfort with it. He refused to take further treatment.

*Comment:* The maximum breathing capacity increased 130 per cent after pneumoperitoneum induction. This excellent result obtained despite a well established compensatory emphysema of over two years duration.

*Case 2:* A 28 year old white male who had undergone right lower lobectomy three years prior to the time we first saw him. Because of postoperative complications with an unexpendable right upper lobe the pneumonectomy was completed approximately one month later. Because of the emotional instability of this patient plus the fact that he had become addicted to drugs, the operating surgeons decided against the performance of a thoracoplasty. Examination revealed that he was extremely short of breath. His mediastinum was retracted into the right hemithorax and there was marked overdistention of the left lung. His maximum breathing capacity was 24 liters per minute and his walking ventilation was 18 liters per minute. It was felt that thoracoplasty would conceivably help but in light of his previous behavior following surgery it was thought hazardous. Pneumoperitoneum was initiated and followed with refills at three day intervals until it became stabilized. At the end of 10 days his maximum breathing capacity was 38 liters per minute and his walking ventilation was  $15\frac{1}{4}$  liters per minute.

*Comment:* The 58 per cent increase in the maximum breathing capacity was accompanied by a two and one-half liter drop in the walking ventilation indicating increased ventilatory efficiency.

*Case 3:* A 38 year old white male who was admitted to the hospital with severe hemoptysis. Subsequent workup revealed bronchiectasis of all segments in the left lung and, in addition, there were asthmatic type wheezes present throughout the entire right lung. This patient's maximum breathing capacity was 36 liters per minute and his walking ventilation was 16 liters per minute. It was felt that he should undergo left pneumonectomy but the condition of his other lung posed a serious problem as far as its ability to carry the breathing load was concerned. Differential bronchspirometry showed that 85 per cent of his function was obtained from his right lung and 15 per cent from his left lung. He was given a short course of ACTH which increased his maximum breathing capacity to 46 liters per minute. The asthmatic wheezes were no longer present in the right lung. He underwent left pneumonectomy and 10 days following his maximum breathing capacity was 39 liters per minute. He was advised to have thoracoplasty on his left side but he refused to give permission for this operation. Two months following surgery x-ray films revealed that the mediastinum had shifted considerably to the left side. No asthmatic wheezes were present on the right side but he began to experience shortness of breath on mild exercise. Maximum breathing capacity was 32 liters per minute. He finally gave consent to have thoracoplasty performed and seven ribs were subsequently removed subperiosteally. Six weeks postthoracoplasty his maximum breathing capacity was 44 liters per minute and his walking ventilation was 15 liters per minute and he was able to perform relatively strenuous activity without being short of breath.

*Comment:* This patient illustrates the often abrupt onset of compensatory emphysema following pneumonectomy. His prompt improvement following thoracoplasty at a relatively early postpneumonectomy date was gratifying.

*Case 4:* This 42 year old white female had undergone a radical mastectomy on her left side in 1948 for carcinoma of the breast. She was treated with deep x-ray immediately after operative convalescence and has remained essentially well until June 1951, when she developed cough productive of purulent secretions, shortness

of breath, anorexia and weight loss. These symptoms became progressively worse and she was first seen by us in the middle of July 1951. Examination at that time revealed a destroyed left lung and subsequent workup failed to reveal evidence of metastatic disease. It was felt that she suffered severe radiation damage to the left lung and left pneumonectomy was advised. Surgical specimen revealed diffuse interstitial pulmonary fibrosis and fibrous obliterative endarteritis—both consistent with irradiation fibrosis. No attempt was made to obliterate the postpneumonectomy space.

Prior to pneumonectomy the vital capacity was 1.2 liters or 41 per cent of predicted normal. A vital capacity in three seconds was 1.1 liters or 92 per cent of her total vital capacity. Six months postpneumonectomy her vital capacity was 1.3 liters and her three second vital capacity was 1.1 liters indicating no loss of function following the surgical procedure. Despite this finding, she stated that she had become short of breath and x-ray films revealed the trachea to be shifted considerably into the left chest. Dyspnea persisted and she became troubled with chronic, although non productive, cough. These symptoms persisted and it was decided to perform thoracoplasty in an attempt to alleviate dyspnea. This was done in July of 1952, when a limited five rib upper thoracoplasty was performed. She made an uneventful convalescence and stated that her breathing was markedly improved. Ventilatory studies carried out four months postthoracoplasty revealed that her vital capacity was 1.3 liters; that her one-second vital capacity was 0.4 of a liter and that her three-second vital capacity was 1.1 liters. Her maximum breathing capacity was 40 liters per minute and her air velocity index was 0.92. At the time of these studies she was free of cough and had no dyspnea carrying out her normal activities.

*Comment:* No significant change in measureable function occurred at any stage of this patient's course yet dyspnea was no longer a problem following thoracoplasty. Whether the relief of dyspnea was due to the disappearance of cough, or whether another mechanism which produces dyspnea—immeasurable from a function standpoint—is present, is open to conjecture.

*Case 5:* This 63 year old white male consulted us for extreme shortness of breath. He had been told that he had pulmonary tuberculosis and was retired from his job 10 years ago for this reason. Subsequently he had been treated for "asthma".

X-ray films revealed both upper lobes to be markedly contracted and fibrosed with associated compensatory emphysema of severe degree. The supraclavicular areas were deeply retracted. Fluoroscopy revealed poor diaphragmatic and rib cage motion and laboratory studies showed the presence of acid fast organisms in the sputum.

The vital capacity was 2 liters or 45.5 per cent of the predicted normal. The vital capacity in three seconds was 1.2 liters or 60 per cent of the total. He was short of breath and had great difficulty in walking even a short distance on a flat surface.

Bronchoscopy revealed marked upward retraction of both upper lobe bronchi. The segmental divisions of the left lower lobe could not be visualized due to marked distortion of the bronchial tree secondary to contraction of the left upper lobe.

It was felt that he was not a suitable candidate for definitive treatment of his bilateral upper lobe fibroid tuberculosis and, therefore, pneumoperitoneum was induced solely to alleviate his severe compensatory emphysema.

Following induction of pneumoperitoneum he noted considerable improvement in ability to breathe. He was subsequently discharged to a sanatorium where pneumoperitoneum refills were maintained. Two months following the induction of pneumoperitoneum his vital capacity was 2.5 liters or 58 per cent of predicted normal. His vital capacity in one second was 0.7 of a liter and in three seconds 1.8 liters (72 per cent of total vital capacity).

*Comment:* This patient has experienced a 25 per cent increase in vital capacity and 50 per cent increase in three second vital capacity, following the alleviation of some of his compensatory emphysema. Although he had no surgery it is felt that the problem of overdistention secondary to shrunken lobes is essentially the same phenomenon noted in postpneumonectomy overdistention.

### *Discussion*

Overdistention of the lung can and does occur whenever there is loss of lung substance following extirpative surgery. It may also occur with loss of lung substance from diseased states. It is a problem more in degree than in kind, and presents symptoms only when the loss of lung substance is relatively large. In the postpneumonectomy state there is often a considerable increase in the lung volume of the remaining lung and this increase is roughly parallel to the increase in the residual air.<sup>2</sup>

There is evidence<sup>6</sup> to show that the development of scoliosis after thoracoplasty results in a marked decrease in ventilatory function. On the other hand, maintenance of pneumothorax in the postpneumonectomy space entirely prevents overdistention and conversion of pneumothorax to oleothorax apparently causes no alteration of pulmonary function or lung volume.<sup>2</sup>

Pneumoperitoneum has not been extensively studied as a therapeutic means of combating postsurgical overdistention, but it would appear to be a valuable adjunct to the treatment of this condition. Its chief disadvantages are that it requires long term maintenance and is poorly tolerated by some individuals. Pneumothorax also shares the disadvantage that it has to be continuously maintained.

Thoracoplasty appears to us to be the most attractive therapeutic device because it does not have to be maintained and because it does not involve the use of foreign bodies, e.g. air, oil, or plastic prosthesis—all of which carry potential hazards. The use of modified thoracoplasty in which the first rib and the transverse processes are left intact minimizes the amount of scoliosis which is in part, at least, responsible for decreased ventilatory function.

### SUMMARY

1) Pulmonary overdistention is not always an irreversible process. Therapeutic response may be obtained even when overdistention has been established over relatively long periods of time.

2) The clinical improvement in patients who have overdistention has been documented by improvement in ventilatory function studies in four patients.

3) Clinical improvement in one patient which was not evident by improvement in ventilatory function studies suggests that occasionally there are other, immeasurable, factors to be dealt with.

4) The prevention of overdistention is to be preferred rather than treating overdistention once it has developed.

5) Modified space obliterating thoracoplasty appears to be the most effective and desirable procedure to prevent overdistention.

6) The efficacy of pneumoperitoneum has been demonstrated and, we believe, that it has a therapeutic place in our armamentarium.

### RESUMEN

1) La sobredistensión pulmonar no es siempre un proceso irreversible. Puede obtenerse una respuesta terapéutica aún cuando la sobredistensión se ha establecido por períodos relativamente largos.

2) La mejoría clínica de los enfermos con sobredistensión, se ha hecho evidente por estudios de la función ventilatoria en cuatro enfermos.

3) La mejoría clínica en un enfermo en el que no pudo ponerse en evidencia mejoría de la función ventilatoria, sugiere que en algunos casos hay otros factores, no estimables, que intervienen.

4) La prevención de la sobredistensión, es de preferirse al tratamiento de ella una vez instalada.

5) La toracoplastia, obliterando el espacio, parece ser el medio más apropiado y deseable para evitar la sobredistensión.

6) Se ha demostrado la eficacia del neumoperitoneo y, creemos, que tiene un lugar terapéutico entre los recursos útiles.

### RESUME

1) L'hyperexpansion pulmonaire n'est pas toujours un processus irréversible. On peut obtenir des succès thérapeutiques même quand l'hyperexpansion existe depuis une période relativement longue.

2) L'amélioration clinique chez les malades atteints d'hyperexpansion pulmonaire a été confirmée par les progrès de la fonction respiratoire qui a pu être étudiée chez quatre malades.

3) L'existence de progrès cliniques chez un malade pour lequel la fonction ventilatoire n'avait pas semblé améliorée, fait entrevoir qu'il faut compter avec des facteurs impossibles à mesurer.

4) Il vaut mieux prévenir l'hyperexpansion que la traiter lorsqu'elle se développe.

5) La thoracoplastie semble être le procédé le plus efficace et le plus souhaitable pour éviter l'hyperexpansion. Grâce à elle, on obtient l'oblitération de la cavité dans laquelle le poumon a tendance à se développer anormalement.

6) On a démontré l'efficacité du pneumopéritoine, et les auteurs lui attribuent une certaine place dans l'armement thérapeutique.

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# Pericardial Coelomic Cyst

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Although slightly more than 60 surgically proved cases have been reported in the English literature, pericardial coelomic cyst remains a relatively rare condition. In the interval since Pickhardt's description in 1934<sup>1</sup> of the first successful removal of such a tumor until the present, internists, surgeons, and radiologists have become more cognizant of this form of cystic disease within the chest. The reader's time will not be consumed by a lengthy review of the literature on the subject. He is referred to excellent papers by Cushing,<sup>2</sup> Lambert,<sup>3</sup> Bradford, Mahon and Grow,<sup>4</sup> Lillie, McDonald and Clagett,<sup>5</sup> Bates and Leaver,<sup>6</sup> Forsee and Blake,<sup>7</sup> and others. A case which recently came under our observation which was diagnosed pre-operatively, will be reported.

## *Case Report*

N. R., a white female, age 28 years, employed as a medical secretary, complained of a moderately severe cold in her chest early in November 1951. This was accompanied by sharp, pleuritic pains in the lower right chest posteriorly and a severe non-productive cough. She had had a previous attack of pleurisy 12 to 13 years ago but could not remember on which side it has occurred. Other than this, there was no history of previous respiratory or cardiac illness. Her past history revealed an appendectomy in 1931, a tonsillectomy and adenoidectomy in 1932, and removal of an ovarian cyst with lysis of adhesions in 1947. Physical examination at the time of the current illness disclosed a few rales and a friction rub over the lower right chest posteriorly. There were no changes in breath sounds or physical signs over the anterior chest on either side. There was no fever.

Radiographic examination of the chest on November 14, 1951 in the postero-anterior and right lateral projections showed both diaphragms normal in contour. The heart was not enlarged. The left lung was clear. The right lung showed a sharply circumscribed shadow of homogeneous density, measuring about 4 x 5 x 7 cm., in the cardio-phrenic angle, lying in contact with the cardiac shadow and the anterior chest wall. The posterior border of the density was rounded and well-defined but the lateral border faded out gradually toward the periphery of the lung field. No fluid-levels or calcium densities were noted in the area involved.

The patient was sent home to bed and placed on terramycin. Re-examination on November 16, 1951 (Figure 1), showed no discernible change in the density of the lesion in the right cardio-phrenic angle but there was noted slight blunting of the costo-phrenic angle posteriorly with minimal hazy density in this area suggesting acute pleurisy. She returned to work one week after the first x-ray films were made, feeling much improved but still having some cough and slight chest pain posteriorly on the right side.

A previous single postero-anterior film of the chest (Figure 2), made sometime in the summer of 1948 was obtained. This film revealed a similar density in the same location as on the current film. It was less well-defined, however, and the chest was reported at that time as showing no abnormality. On December 24 1951 the chest was re-x-rayed, and the tumor mass appeared unchanged. The

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minimal pleural changes posteriorly had cleared. A radiographic diagnosis of pericardial coelomic cyst was made.

On January 8, 1952 the patient was admitted to the Buffalo General Hospital, and on January 10, 1952 right thoracotomy was performed. The operative report follows:

With the patient on the left side, a right antero-lateral incision was made along the sixth interspace and the thorax was opened. Digital exploration revealed a cystic structure lying in the lower anterior mediastinum. A segment of the fifth rib at the costo-chondral junction was removed and rib spreaders inserted. The cystic structure, measuring about 2x5 inches, could then be visualized. It was smooth, rounded and lay over the dome of the right diaphragm, being attached at the cardio-phrenic angle. With gentle traction on the cyst, it was apparent that it was arising from the pericardium to which it was attached by a broad base measuring approximately one and one-half inches in diameter. By means of careful, sharp dissection, and after the mediastinal pleura on the anterior surface of the cyst was incised, a line of cleavage was obtained. The cyst was then gently dissected from the pericardial attachment after severing the pleura around the entire circumference of the cyst. It was removed intact and was smooth, glistening and appeared translucent. There were a few bleeding points at the edge of the pericardium. These were clamped and tied with plain catgut ligature. Inspection showed adequate hemostasis, and the thorax was closed in the usual manner. A snug dressing was applied.

The pathological examination of the specimen (Figure 3), showed an ovoid, thin-walled, transparent cystic structure which measured 8x5x4 cm. There was one small amount of fat tissue attached to the surface in one area. Microscopic sections through the wall showed a serous cyst with a thin, fibrous wall lined by simple columnar and flattened epithelium.

The early post-operative course was uneventful except for the usual discomfort in the operative region. An x-ray film on January 14, 1952 showed the left diaphragm clear and regular. The right diaphragm was elevated and there was some



FIGURE 1A

FIGURE 1B

Figure 1A: Postero-anterior film of the chest made November 16, 1951. The upper margin of the cyst is indicated by arrows.—Figure 1B: Right lateral film of the chest made November 16, 1951. The typical location of the cyst in the anterior mediastinum is clearly shown.

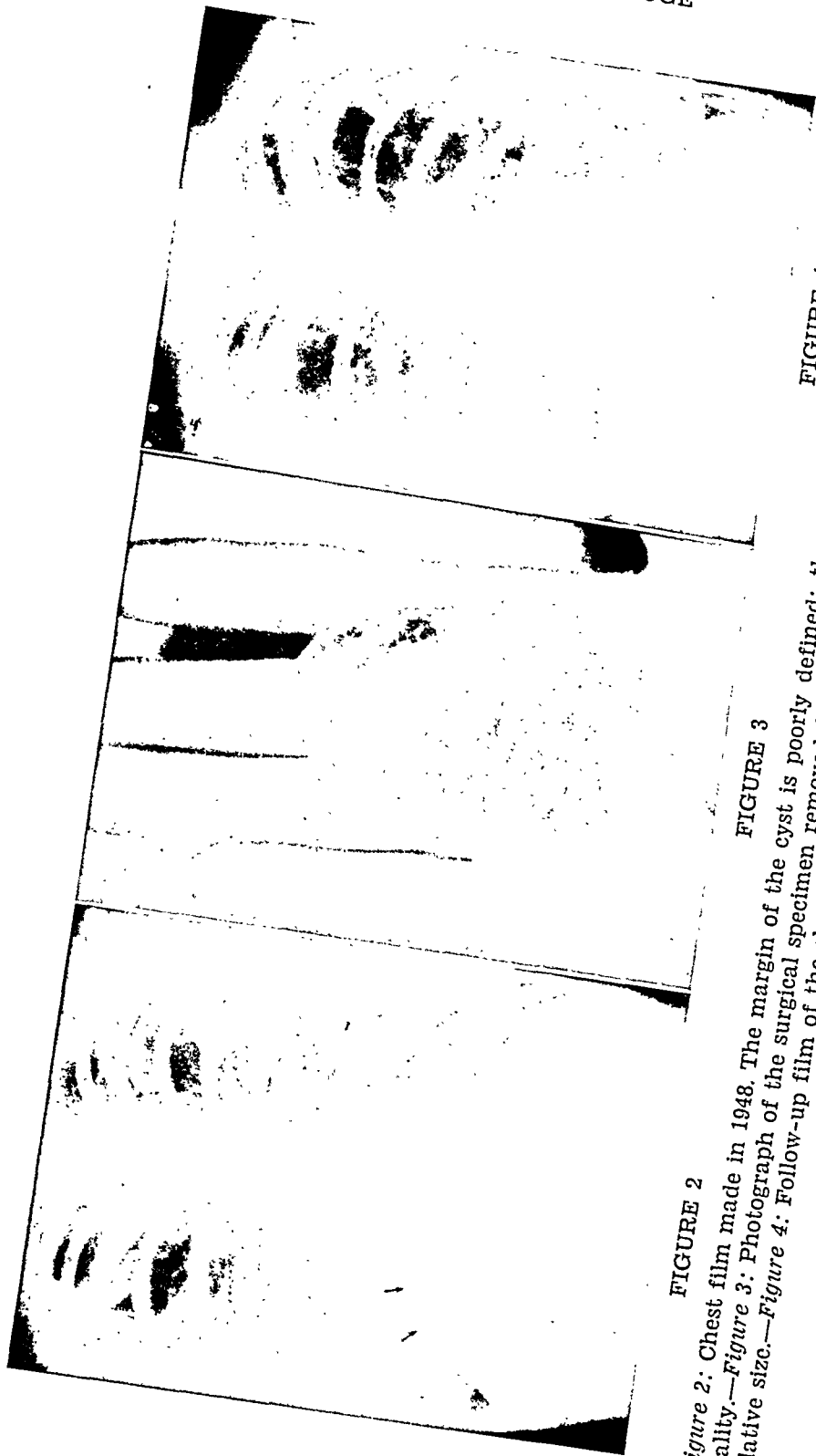


FIGURE 2

Figure 2: Chest film made in 1948. The margin of the cyst is poorly defined; the film was read as showing no abnormality.—Figure 3: Photograph of the surgical specimen removed from the right hemi-thorax January 10, 1952. Note its relative size.—Figure 4: Follow-up film of the chest made August 4, 1952.

FIGURE 3

FIGURE 4

pleural density overlying which probably represented a small amount of pleural fluid. The lung above was expanded and clear. The left chest was clear. On January 19, 1952 the pain in the right chest became severe and knife-like in character. An x-ray film on January 21, 1952 showed a slight increase in the amount of pleural density at the right base but there was no appreciable mediastinal shift. The left lung remained clear. The temperature curve was essentially normal except between January 22 and January 26, when it varied between normal and 101 degrees F. A blood count on January 24, 1952 showed 4,000,500 erythrocytes, 15.6 gms. of hemoglobin, and 10,000 leukocytes with a differential count of 12 bands, 76 filaments, 11 lymphocytes, and one monocyte. A chest film made on January 26, 1952 showed considerable increase in the amount of fluid in the right pleural space which filled in almost half of the hemi-thorax. There was no appreciable mediastinal shift. The left lung remained clear. On the same day 750 cc. of clear, amber fluid were removed from the right chest. This was cultured but showed no growth of organisms. After the thoracocentesis, she gradually became afebrile, breathing became less labored, and her chest pain diminished. She was discharged on February 2, 1952 feeling much improved but still having some residual pleural pain on the right side. A follow-up film of the chest made on August 4, 1952 showed slight elevation of the right diaphragm and minimal blunting of the costo-phrenic angle (Figure 4). Both lung fields were clear and the heart and mediastinum were not displaced.

### *Discussion*

Pericardial coelomic cyst is more often than not a silent lesion. It is usually disclosed, as in this case, by radiographic examination of the chest as a routine measure or in search of evidence of other forms of disease or injury. Earlier writers stated that the condition produced no symptoms. However, as more and more cases were reported, it became apparent that many patients not only gave a history of one or more symptoms but that they also experienced partial to complete relief after surgical removal of the tumor. Lillie, et al.<sup>5</sup> reviewed 12 cases from the Mayo Clinic between 1941 and 1947, of whom six were asymptomatic. The remainder had such complaints as dyspnea, sub-sternal pain on exertion, "fluttering" of the heart, a tight feeling in the chest, tachycardia and precordial pressure, dull intra thoracic pain of long duration, and pressure over the heart after eating. Bradford, et al.<sup>4</sup> reported eight cases, of which three had varying symptoms of pain in the chest, dyspnea, productive cough, and vague pains in the left upper quadrant of the abdomen which occurred after eating and became more severe on lying down. In Forsee and Blake's series of 11 cases,<sup>7</sup> six had symptoms referable to mediastinal pressure or alteration in the normal pulmonary or cardiac physiology. Lam's case,<sup>8</sup> in which the tumor was unusually large, had a 10 year history of dyspnea, fatigue and angina pectoris, and was thought to have congenital heart disease. She made an excellent recovery after removal of the cyst with disappearance of symptoms. Reports of other authors describe symptom-complexes of a similar nature as those mentioned above.

Except in those cases with extremely large tumors, physical signs are notably lacking, even though the shadow on the roentgenogram is of sufficient size to be clearly visualized. Changes in percussion note are minimized because of the lesion's proximity to the heart, and are therefore



of little help in physical diagnosis. Auscultation is valueless, as any tumor or mass containing static fluid precludes the production of a bruit or adventitious sound.

It is, therefore, the chest roentgenogram which gives us the most valuable signs from which the condition may be suspected. Postero-anterior and lateral films usually suffice for good visualization of the lesion, but oblique and lateral decubitus projections may yield additional and helpful information. The exposures should be made at the point of maximum inspiration. Even a slight elevation of the diaphragm may minimize the density cast by the cyst, resulting in its being unobserved. This was the experience in our case, as the condition was not suspected from the film made in 1948.

Most characteristically, a pericardial coelomic cyst appears on the chest film as a round or ovoid shadow of homogeneous density, lacking in any calcific elements, which is situated in the anterior mediastinum at one of the cardio-phrenic angles. The mass is sharply defined on at least one projection even though it may appear to blend with the lung parenchyma in other views. It intimately approximates the anterior chest wall or diaphragm, or both, resembling a localized collection of encapsulated fluid. A most important feature is that it is always in contact with the cardiac silhouette. Lillie, et al.<sup>5</sup> state that two-thirds of the cases reported occurred at the cardio-phrenic angles, with the remainder lying at a higher level in the anterior mediastinum. Twice as many occur on the right side as on the left. Of the right-sided lesions, 75 per cent or more are situated at the angle. Of the left-sided lesions only about 40 per cent show a predilection for this same location.

Until the publication of Lambert's paper in 1940,<sup>3</sup> in which he presented two cases of Dr. Frank Berry and one of Dr. E. F. Butler, the pathogenesis of pericardial coelomic cysts was not well understood. His theory as to their origin is currently accepted as the most plausible, and, undoubtedly, is the correct one. A verbatim reiteration of what he has so precisely written is superfluous but his thought might be crystallized in a few words. When one of the primitive lacunae, which develops from the mesenchymn both lateral and ventral to the primordial ectodermal plate, fails to fuse with the remainder to form the pericardial coelom, it develops into an independent cavity or cystic structure attached to the pericardial coelom. Grossly, such a cyst appears as a smooth, thin-walled, glistening tumor mass, spherical in shape, and containing a watery, serous fluid which renders it almost transparent. The mass is covered with mediastinal pleura and is attached to the pericardium by a pedicle or base of varying size through which it receives its blood supply. At surgery, the cyst is seen to be entirely free of the adjacent portion of the lung and a distinct line of cleavage may be found between it and the pericardium, making enucleation an easy procedure. The significance of this fact will be mentioned in the discussion of a differential diagnosis. Microscopically, the cyst wall is composed of fibrous or collagenous tissue containing a few scattered

lymphocytes and vascular channels. The lining membrane consists of a single layer of cuboidal to flattened epithelial cells morphologically similar to the mesothelial cells lining the pericardium.

As many cystic tumors are located in the mediastinum a differential diagnosis is worthy of mention. To be considered are all the congenital lesions, namely, epidermoid, dermoid, teratoid, bronchial, esophageal, gastro-enteric cysts and cystic lymphangioma as well as the more common varieties of lipoma, echinococcus cyst and eventration of the diaphragm. Occasionally rare malignant lesions produce somewhat similar shadows on the roentgenogram. Bates and Leaver<sup>6</sup> reported two such cases, one of which proved to be a spindle-cell endothelioma and the other a probable papillary adenocarcinoma of undetermined origin.

The epidermoids are lined with stratified epithelium and their walls are made up of dense fibrous tissue, with or without glands of ectodermal origin. They are filled with a clear or milky fluid, or with a gelatinous material frequently mixed with hair. Dermoids are of a similar nature but in addition to the ectodermal structures exhibit tissues of mesodermal origin such as cartilage, bone, teeth, or smooth muscle. The teratomas are usually more solid in nature, and show histological elements of all three primary germ layers. Glandular elements of the alimentary and respiratory tract, as well as ectopic thyroid and thymic tissue may be found in addition to the contents of dermoids as mentioned above. Bronchial, esophageal and gastro-enteric cysts show a histological structure resembling that of the normal viscus. Cystic lymphangioma differs little microscopically from pericardial coelomic cyst except that on occasions cholesterol crystals are found in the fibrous wall. Grossly, there are singular differences. The lymphangiomas are multilocular tumors, intimately adherent to all surrounding structures, especially the pulmonary tissue. They receive their blood supply from adjacent tissues over their entire surface area. This fact makes complete extirpation almost impossible because the profusely bleeding vascular bed produces a serious surgical problem. Echinococcus cysts show a characteristic lining membrane which readily identifies them. They too, are often multilocular. Lipoma and eventration of the diaphragm often cannot be differentiated from a cystic structure.<sup>9</sup>

Of all the above mentioned lesions, only the dermoids and teratomas may, on occasion, show roentgen evidence of their contents. One can readily understand then, that a positive pre-operative is impossible. This can be achieved only by removal of the tumor and pathological examination of the specimen. With intra-tracheal anaesthesia, in which intra-pulmonary pressures may be accurately controlled and varied at will, giving the surgeon ample operating room, such cysts may be easily and safely removed. Even though all the evidence at hand is strongly presumptive of a pericardial cyst, and even though such a lesion is always benign, the low morbidity and mortality rate makes exploration imperative. The error of procrastination, should the suspected lesion be malignant, can never be rectified and may cost the patient his life.

## SUMMARY

A case of pericardial coelomic cyst which was diagnosed pre-operatively is reported. The varied symptomatology, the paucity of physical signs and the importance of the roentgen findings are discussed. The pathogenesis of such cysts and their differential diagnosis is briefly reviewed. Inability to establish a positive diagnosis in all cases stresses the fact that surgical removal should be the only accepted form of treatment.

## RESUMEN

Se relata un caso de quiste pericárdico celómico que fué diagnosticado antes de la operación. Se discuten la sintomatología variada, la escasez de signos físicos y la importancia de los hallazgos radiológicos. La incapacidad de hacer el diagnóstico en todos los casos recalca el hecho de que extirpación quirúrgica es la única forma de tratamiento.

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-

## Post-Graduate Session—Compensation Court

THEODORE H. NOEHREN, M.D., F.C.C.P.\*

Buffalo, New York

Concentrated lectures and panels in a postgraduate course produce returns that diminish in proportion to the length of the course. Introduction of student participation sessions can often refresh the interest of the group. A class compensation board, using compensation cases from the files of previous years, offers a method of developing this student participation. Pulmonary diseases lend themselves nicely to such a method of presentation.

While a great many compensation judgements rest on legal details, the basic principles of disease are of fundamental importance. In silicosis, for example, each state may have its own legal attitude toward the disease, but basic to that are certain medical pre-requisites. Such pertinent medical factors include, (1) length and type of dust exposure, (2) roentgenologic vs. clinical diagnosis of the disease, (3) symptomatic vs. asymptomatic silicosis, (4) progression of the disease, (5) prognosis, (6) relation to further irritants, (7) rehabilitation, (8) relationship to tuberculosis and other pulmonary diseases, and many others. The major testimony and conflicts in compensation cases are medical, with physicians the principle witnesses.

Other pulmonary diseases viz. spontaneous pneumothorax, malignancy, bronchiectasis, the fungus diseases, siderosis, berryliosis, Shaver's disease, bagasse disease and chest trauma are diseases appearing frequently before the compensation boards of the country. Like silicosis, they lend themselves to a class consideration of this sort.

The method we have employed is to use actual cases from the files of the State Compensation Board, and present the plaintiff's cause and his x-ray findings for the student court to consider. Many of the group are frequently willing to pass judgement without any further clinical data or investigation. Others, however, with greater knowledge of the disease, rise to the occasion and suggest further pertinent medical considerations—an effective way to emphasize the significance of such information. This in turn, can be developed into a rather active discussion of the disease involved. Concern for the rights of the patient serves as the human-interest catalyst to the discussion.

The crux of each case has been in having the compensation commissioner himself present to give and explain the final decision of the State Board and the reasons for that decision. This too, while it may involve some legal technicalities, frequently adds further pertinent medical considerations of the disease in question.

---

\*Assistant Professor of Medicine, University of Buffalo School of Medicine and Department of Medicine, Buffalo General Hospital.

The tenth in a series of articles prepared under the sponsorship of the Council on Undergraduate Medical Education of the American College of Chest Physicians.

This approach has several advantages, the first of which is class participation which can be refreshing and quite enjoyable. The group, with moderate assistance, serves to teach itself, just as group therapy is effective with patients. It also promotes the airing of misimpressions, and correction of such misinformation is as important as acquiring new material (a side of postgraduate teaching that is usually overlooked).

This approach also serves well to introduce an interest in pulmonary diseases to physicians not primarily concerned with that specialty. Medical specialization has developed an unfortunate segregation of medical thought which is reflected and overemphasized in medical meetings and courses. We spend a good deal of time talking to ourselves and to men with similar experiences and interest. This compensation court method offers one means of cutting across specialty lines. Our own presentation has been for an occupational hygiene course intended for industrial physicians, many of whom do not attend chest sessions as a rule.

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# Editorial

## CYTOLOGIC DIAGNOSIS OF LUNG CANCER

SEYMOUR M. FARBER, M.D., F.C.C.P.  
San Francisco, California

The application of cytologic techniques to the diagnosis of cancer of the lung is about seven years old; the accumulation of substantial clinical studies since 1947 have demonstrated that cytology deserves to be considered one of our primary diagnostic techniques for this disease. Nevertheless, there are an insufficient number of laboratories utilizing this technique.

This neglect is unfortunate and, further, difficult to understand. At the present time, cytology promises morphologic diagnosis of perhaps twice the percentage of lung cancers that are now so diagnosed by bronchoscopy; further, a greater percentage of cancers diagnosed by cytology are amenable to surgery than those diagnosed by bronchoscopy. The method is very easily applied by the physician, and it is relatively inexpensive. The equipment it requires is already on hand in every laboratory. It requires two things: (1) That a laboratory technician undertake three or four months training in a laboratory where the method is already practiced, and, (2) That a pathologist become thoroughly acquainted with cytologic appearances, which differ from those seen on tissue sections.

One suspects that the reluctance to establish facilities for cytologic diagnosis of lung cancer is a part of the lethargy which one frequently meets when the subject of lung cancer is introduced. It is true that the mortality rate for this disease remains discouragingly high, however it is approached. On the other hand, one cannot diagnose and treat individual patients in terms of statistics. Five-year survivals have been secured by means of surgery; every patient in whom lung cancer is suspected must be regarded, then, as a potential five-year cure. The medical profession cannot neglect promising diagnostic techniques because the overall recovery rate is low. Statistics are valuable but they cannot be allowed to determine the attitude toward the individual patient.

There is no reason to think that the present application of cytology exhausts its possible service in the diagnosis of lung cancer. In recent series a diagnostic accuracy of 90 per cent has been secured among large series of lung cancer cases. It has been further observed, however, that the efficiency of this method is probably greater among early cases, in which the bronchial passages are not yet occluded, than in late ones. This suggests that the greatest application of cytology may yet prove to be as a routine screen device. Its convenience for the patient and physician and its inexpensiveness make its routine use in annual or semi-annual checkups entirely feasible. Surgical cure rates might be expected to show a major improvement if cytology were so used. Only the lack of facilities and interested personnel prevent us from investigating this possibility.



RICHARD H. OVERHOLT

# Presentation of the College Medal for 1954 to Dr. Richard Hollis Overholt\*

BURGESS L. GORDON, M.D., F.C.C.P.\*\*  
Philadelphia, Pennsylvania

Mr. President, Members of the College, Ladies and Gentlemen:

I am pleased, Dr. Greer, to have the privilege of speaking for the American College of Chest Physicians in the presentation of the College Award to Dr. Richard Hollis Overholt. Among the eight distinguished recipients of this, the highest honor conferred by the College, Dr. Overholt belongs to a small group, hardly more than a dozen, who early in their medical transcendancy made thoracic surgery the major field of endeavor. In adding another illustrious physician to the College hall of fame, the Committee on Award has very appropriately expressed the appraisal, not only of the College, but of other important segments of American medicine.

As I look upon you, Dick, standing here, about to receive this College Medal, I realize that fancy plays an embarrassing trick by carrying me back over quite a few years to the occasion when I first met you. On this particular morning, you were speaking about the potentials of pulmonary resection. Indeed there was skepticism, for there remained the hazards of atelectasis, spreading infection, and faulty anesthesia. It is a matter of great interest that the events proved your concepts to be correct. You have removed with fine precision localized processes of bronchiectasis, tuberculosis, cystic disease, and even cancer of the lung. Your knowledge of anatomy and physiology—your imagination, ingenuity, refined techniques, and careful reporting have won for you the recognition of thoracic medicine and the gratitude of countless patients.

In this College are your friends and associates—some have watched from their vantage point of long experience and the knowledge of pioneer days; many have grown up with you; and not a few have been your pupils and assistants. You have earned our esteem, our confidence and respect.

Dick, I am very happy to hand you the College Medal. Along with it go the admiration and the affection of your fellow members of the American College of Chest Physicians.

## BIOGRAPHICAL DATA

University of Nebraska School of Medicine, M.D., 1926.

Intern: University of Pennsylvania Hospital, Philadelphia, 1926-28.

Fellow in Surgery, University of Pennsylvania Hospital, 1928-31.

Staff, Lahey Clinic, Boston, Massachusetts, 1931-38.

Overholt Thoracic Clinic, 1101 Beacon Street, Brookline, Massachusetts, 1938.

Clinical Professor of Surgery, Tufts College Medical School, Boston, Massachusetts.

Thoracic Surgeon: New England Deaconess Hospital, Boston, Massachusetts.

Consultant: Norfolk County Hospital, Plymouth County Hospital, Cambridge Tuberculosis Sanatorium, Sassaquin Sanatorium, Rhode Island State Sanatorium, Barnstable County Hospital, Essex County Sanatorium, Bristol County Sanatorium, and New England Center Hospital.

President, American College of Chest Physicians, 1948-49.

\*Presented at Presidents' Banquet, 20th Annual Meeting, American College of Chest Physicians, San Francisco, June 19, 1954.

\*\*Chairman, Committee on Awards.



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L. C. Manni, M.D., Medical Director  
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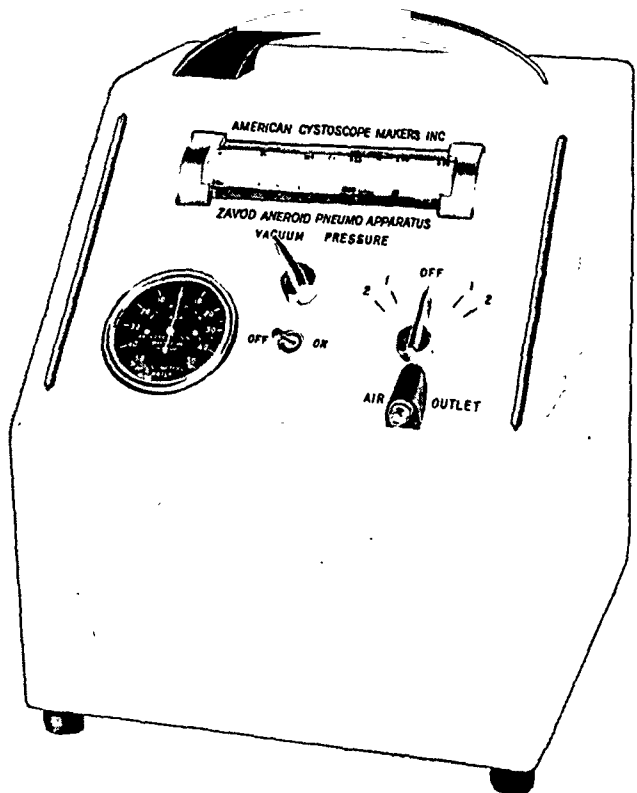
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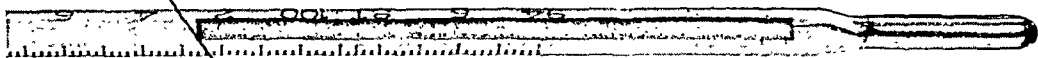
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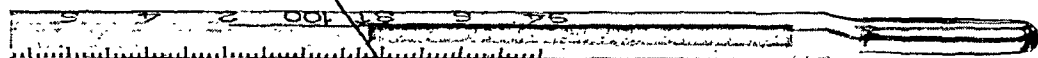
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2. Glatt, M., and Ross, S.: Antibiotics & Chemotherapy 4:395 (Apr.) 1954.

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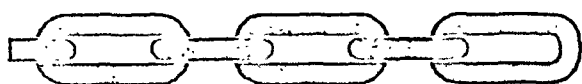
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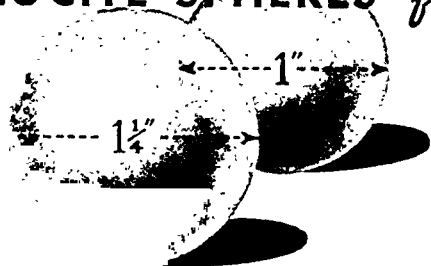
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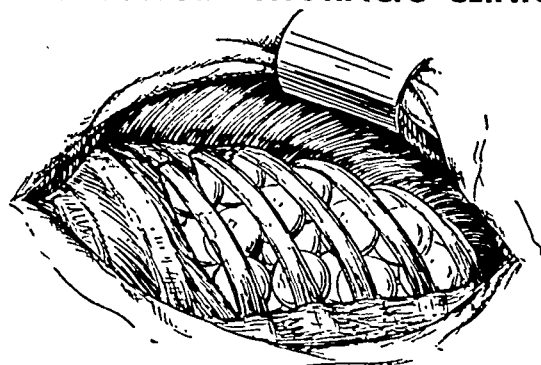
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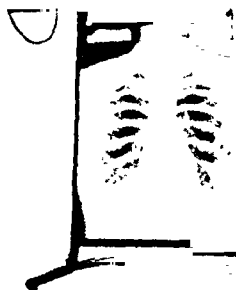
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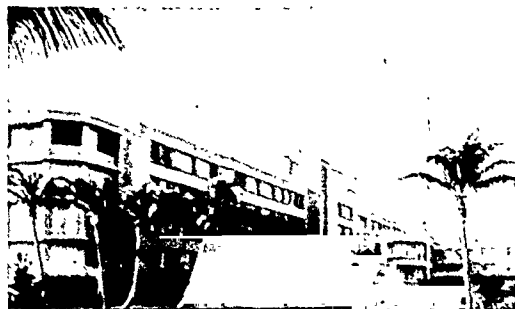
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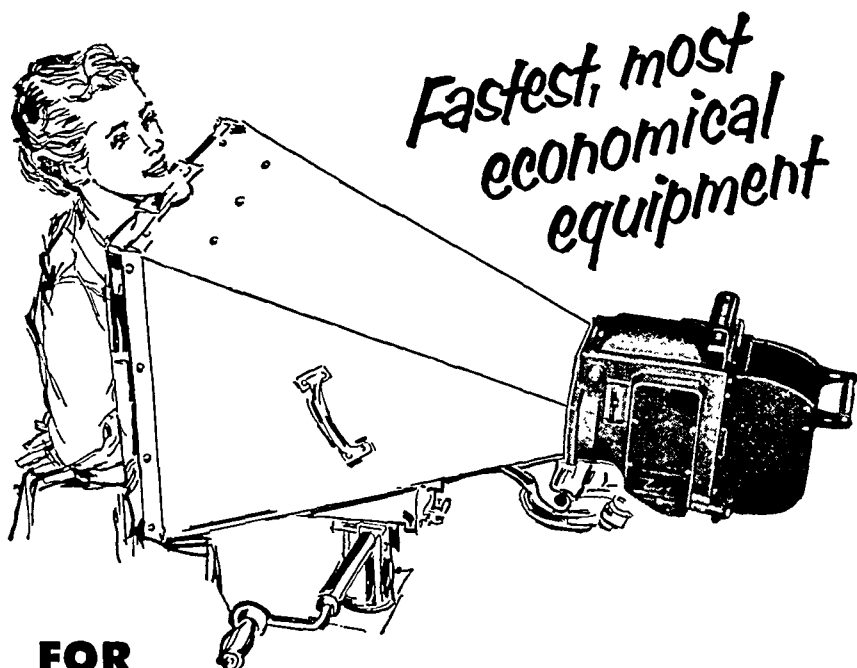
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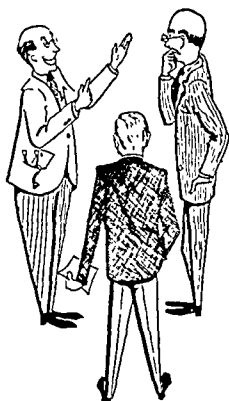
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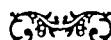
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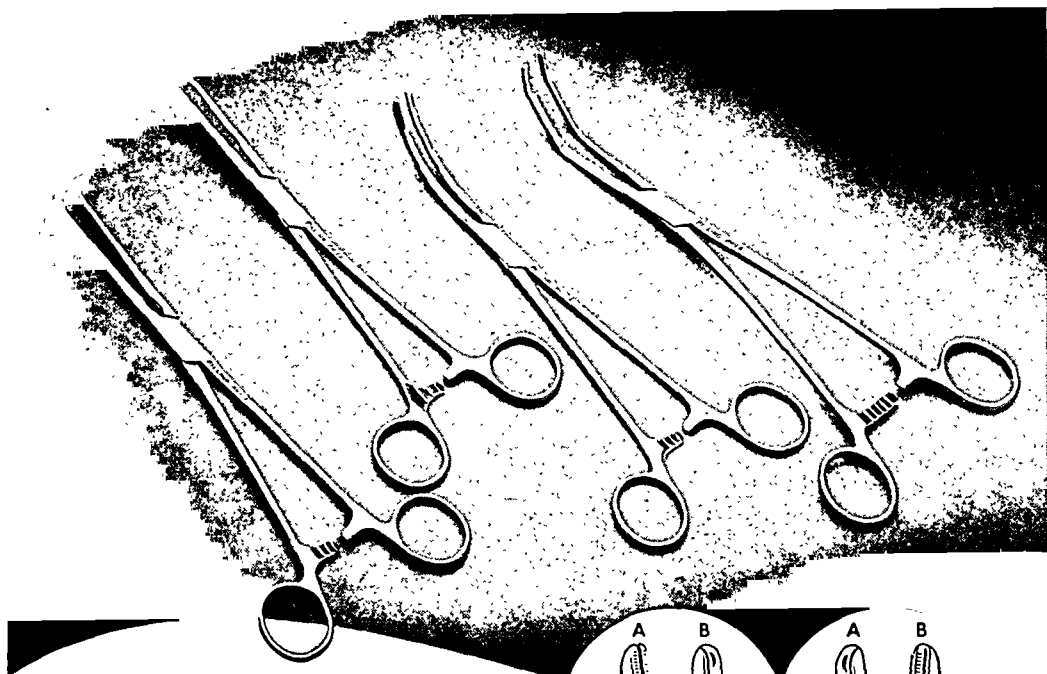
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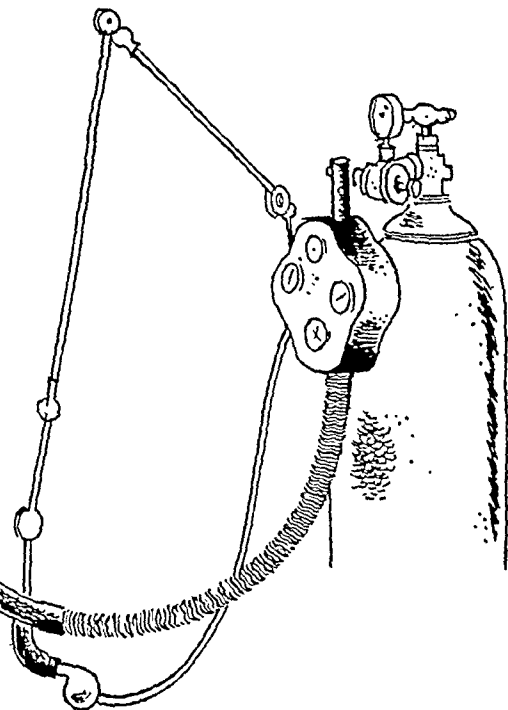
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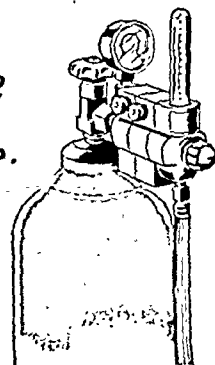


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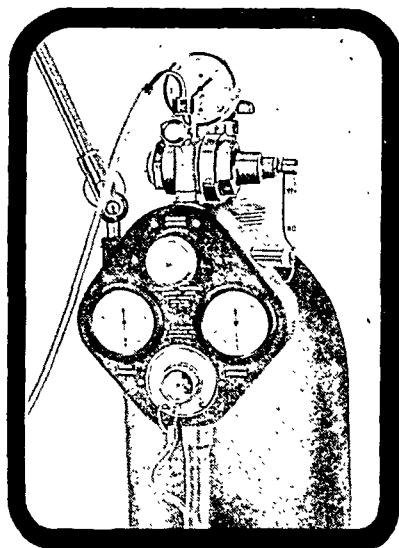
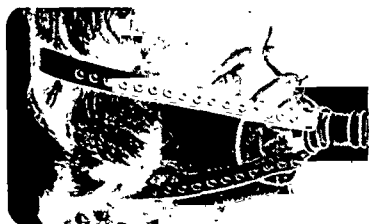
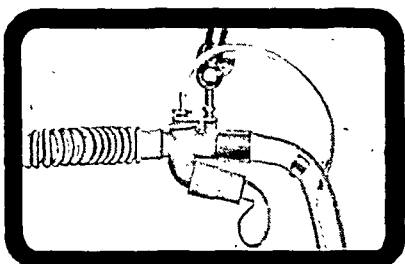
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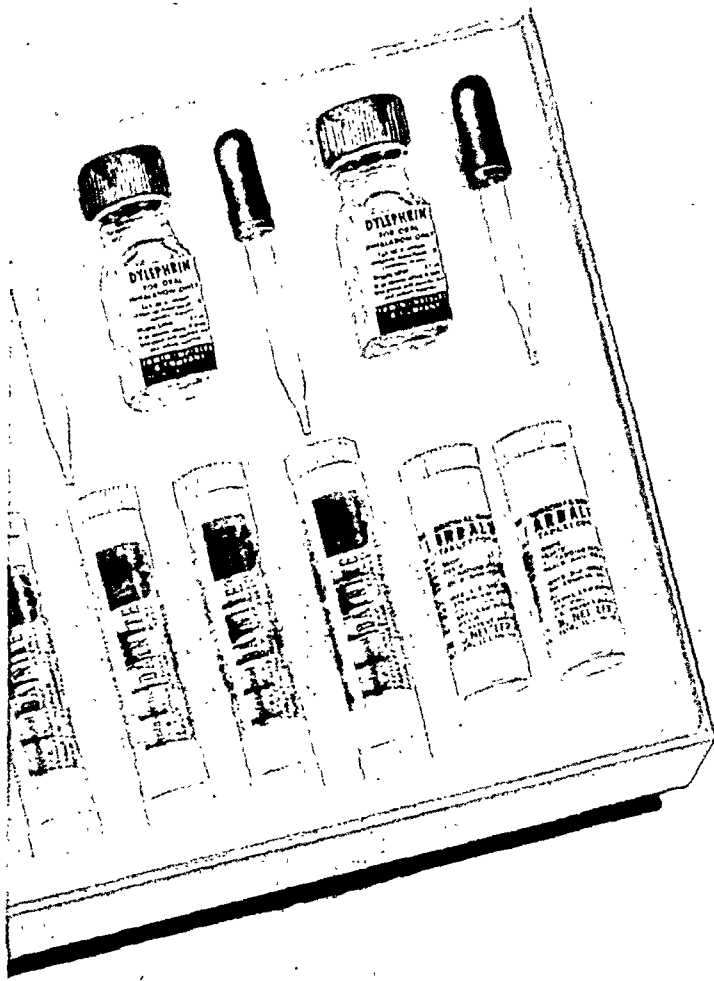
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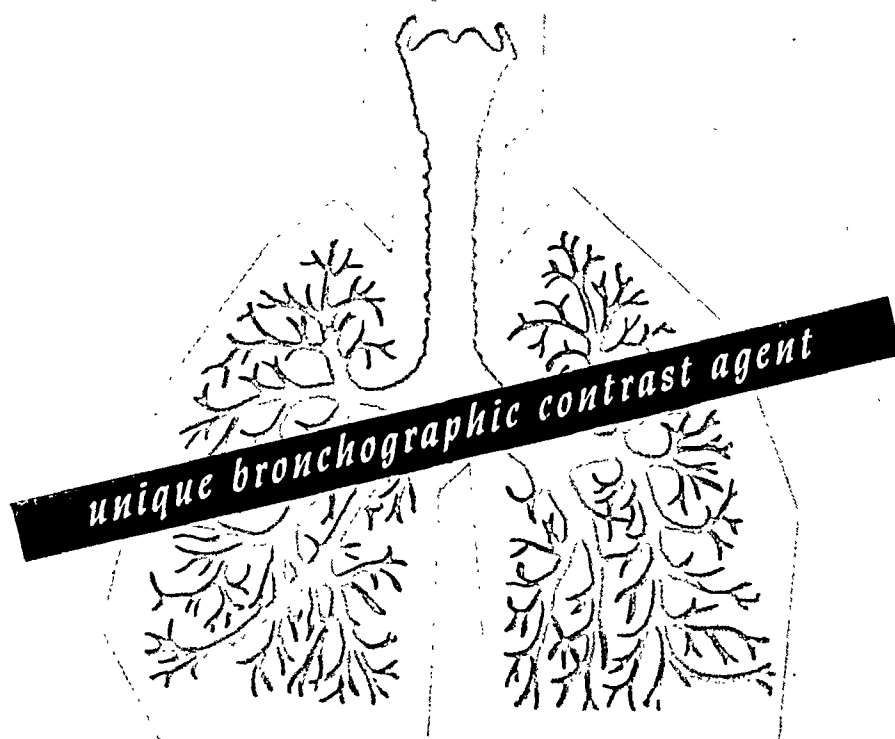
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# DISEASES *of the* CHEST

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VOLUME XXVI

AUGUST 1954

NUMBER 2

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## The Role of Segmental Resection for Bronchiectasis in Conserving Pulmonary Function

RICHARD H. OVERHOLT, M.D., F.C.C.P.,\*

JAMES H. WALKER, M.D., F.C.C.P.\*\* and BENJAMIN E. ETSTEN, M.D.\*\*\*

Brookline, Massachusetts

One of the fundamental principles of surgery is the removal of diseased tissue with all possible preservation of healthy tissue. In thoracic surgery, fulfillment of this principle was not always possible while the pulmonary lobe was the smallest unit of excision. The concept of the pulmonary segment as a unit of excision, and the consequent development of requisite surgical techniques, now extend the scope of safe surgical therapy to cases which heretofore presented contraindicating hazards.

The pulmonary architecture is so well designed that seldom are *all* the segments of any lung involved. Disease before puberty may damage a considerable portion of a lung, but the remaining healthy tissue will so hypertrophy that it can fulfill its physiological requirements, and become important to save. On the other hand, when pulmonary disease occurs in the adult the remaining healthy tissue may become overtaxed by the stress of constant cough and the influence of intimate toxicity. Although such tissue may resist actual infection, it can, by means of compensatory emphysematous change, steadily decrease in its powers of physiological function.

In either of these situations, the best chance the patient has of release from respiratory distress is excision of the disease. Such surgery should be planned and carried out on a segmental basis, and at the optimum time.

Two cases are reported demonstrating the value of segmental resection in conserving pulmonary function.

*Case 1:* Mrs. L.R., age 46, had moderately severe pulmonary hemorrhages five times between April 1949, and May 1950. Bronchography revealed bronchiectasis involving the superior segment of the left lower lobe and the lingula of the left upper lobe. May 17, 1950, a segmental resection of the three involved segments

---

\*Clinical Professor of Thoracic Surgery, Tufts College Medical School; Thoracic Surgeon, New England Deaconess Hospital, Boston.

\*\*Instructor in Surgery, Tufts College Medical School; Thoracic Surgeon, New England Deaconess Hospital, Boston.

\*\*\*Anesthetist-in-Chief, New England Deaconess Hospital and Pratt Diagnostic Clinic; Professor of Anesthesia, Tufts Medical School, Boston.



TABLE I

	<i>L. R., Age 47</i>	<i>A. D., Age 29</i>
Presenting symptoms	Several recurrent pulmonary hemorrhages	Purulent sputum and repeated respiratory infections.
Date of surgery	May 17, 1950	November 17, 1951.
Surgery	Lingula of LUL Sup. seg. LLL	LLL Lingula & ant. seg. LUL.
Post-operative complications	None	None.
Remarks		Left temporary phrenic.
Maximum Breathing Capacity:		
Determined 1/m.	66	84
Predicted Per cent	88	67
Walking Vent.—1/m.	13.9	18
WV/MBC	0.21	0.21
Timed Vital Capacity:		
1 second per cent	78	80
2 seconds per cent	92	90
3 seconds per cent	96	95
Air Velocity Index	0.98	0.90
Vent. Equiv. 1/m.	2.8	2.8
Tidal Vol., cc.	806	748
Min. Vol., 1/m.	8.8	10.4
O <sub>2</sub> Uptake, cc./m.	314	369
Vital Cap., cc.	2120	2932
Funct. Resid. Cap., cc.	1329	1914
Resid. Cap., cc.	918	1044
T. Lung. Cap., cc.	3095	3976
RC/TC—Per cent	30	26
Mixing Index—Per cent N <sub>2</sub>	1.00	1.20
O <sub>2</sub> Sat. Per cent*	97	95
pHs—37 Degrees C.*	7.25	7.45
pCO <sub>2</sub> —mm. Hg.*	48.8	39
Total CO <sub>2</sub> —mm./L*	21.3	26.7
*Determined at rest.		

was done without difficulty. The postoperative course was uneventful and the patient was discharged from the hospital on the 16th day. Since surgery there has been no recurrence of pulmonary bleeding and she has continued to work without difficulty. Fifteen months after surgery pulmonary function studies were performed and are summarized in Tables I and II.

*Discussion:* This patient's clinical problem was recurrent pulmonary hemorrhages coming from bronchiectasis in the left upper lobe and the left lower lobe. If the unit of excision had been lobe instead of segment, it would have been necessary to do a left pneumonectomy as treatment for the pulmonary hemorrhages. The segmental surgery in this patient saved five segments of the left lung.

The results of the ventilatory function studies demonstrate that there is slight impairment to air flow. Total lung volume was 3095 cc. and the residual volume relationship to total lung volume 30 per cent; alveolar nitrogen 1.0 per cent. These figures show that there is an increase in the residual capacity consistent with hyperinflation. The mixing index of 1 per cent indicates that there is no impairment to alveolar air mixing. The differential bronchspirometry findings show that the remaining five segments of the left lung contribute 30 per cent of the total oxygen consumption and 42 per cent of the total ventilation. These five segments indeed contribute at least one third of the total pulmonary function. This case demonstrates the functional value of conservation of healthy pulmonary tissue.

*Case 2:* Mr. A.D., age 29, had a lung abscess and empyema on the left which was treated by open drainage at the age of three years. Following this episode he had chronic cough and raised small amounts of purulent sputum daily. In 1943, while in the service, he had pneumonia and another lung abscess on the left side. Bronchograms in October, 1946, showed bronchiectasis involving the entire left lung with the exception of the posterior-apical segment of the left upper lobe. Between 1949 and 1951, he had blood streaked sputum on two occasions and developed progressive dyspnea.

At exploratory thoracotomy in November 1951, the left lower lobe and the lingula and the anterior segment of the left upper lobes were boggy and contracted. The posterior apical segment of the left upper lobe was several times its normal size. All the diseased tissue was removed leaving only the one segment (posterior-apical) in the left hemithorax. A temporary phrenic crush was done to reduce the volume of the hemithorax. The postoperative course was uneventful and he was discharged on the 13th day. Since surgery he has returned to full time work as a barber and is now free of pulmonary symptoms. In Tables I and II pulmonary function studies were done and are summarized.

TABLE II

	— L. R., Age 47 —		— A. D., Age 29 —	
	Right Lung	Left Lung	Right Lung	Left Lung
Segments remaining	10	5	10	1
O <sub>2</sub> Per cent	70.0	30.0	77.4	22.6
Vent. Per cent	58.1	41.9	72.0	28.0
Vital Capacity Per cent	66.2	33.8	80.0	20.0

*Discussion:* This patient presented us with the unusual opportunity to study the function of one pulmonary segment. This remaining segment was hypertrophied and larger than a normal segment. The diseased units became contracted during early childhood, permitting the non-involved segment to enlarge and hypertrophy during the period of body growth.

The results of the total pulmonary function as measured by the M.B.C., walking ventilation, and timed vital capacity demonstrate efficient function for the number of remaining pulmonary segments. The intrapulmonary mixing and residual capacity were within normal limits.

The most significant findings were that the remaining segment contributed 22.6 per cent of total oxygen consumption and 28 per cent of total ventilation.

The differential bronchspirometry clearly illustrates the functional relationship between the one hypertrophied segment on the left to the 10 normal segments on the right.

The value of conserving a single pulmonary segment is shown by these findings.

#### CONCLUSION

Compensatory hyperinflation of lung tissue following segmental resection does not impair intrapulmonary mixing of gases as shown in both case reports. Pulmonary function of the remaining lung tissue following segmental resection for bronchiectasis is of physiological value.

#### RESUMEN

Tal como se muestra en los dos casos referidos, la sobredistensión compensadora del tejido pulmonar después de la resección segmentaria no perturba la mezcla de gases intrapulmonar. La función pulmonar del tejido restante después de la resección segmentaria por bronquiectasis, es de valor fisiológico.

#### RESUME

L'hyperexpansion compensatrice du tissu pulmonaire faisant suite à la résection segmentaire n'empêche pas le mélange des gaz intrapulmonaires, comme il est démontré dans les deux observations rapportées. La fonction du tissu pulmonaire restant après une résection segmentaire pour bronchiectasie garde sa valeur physiologique.

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# Reversibility of Isoniazid Resistance Developed in Mycobacterium Tuberculosis\*

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## *Introduction*

It has often been demonstrated that patients treated with isoniazid or its derivative, after a certain time or after a certain quantity of medication, develop resistant strains of mycobacterium tuberculosis. This conception is generally accepted. On the other hand it is a well known fact that many cases in whom streptomycin treatment has failed, and streptomycin resistant strains are present, are markedly benefitted by isoniazid treatment. Clinical, radiological and bacteriological improvement, including sputum conversion, occur. There are numerous publications dealing with the reversion of streptomycin resistance; and it has been proved that in some cases the streptomycin resistant strains disappeared following further treatment. It has also been demonstrated in vitro, that isoniazid resistant strains may revert to isoniazid sensitivity.<sup>3</sup>

In this laboratory investigations have been conducted in an endeavor to find out if reversion of isoniazid resistance occurs in vivo. Those patients on isoniazid whose tubercle bacilli developed a certain degree of resistance were watched for several months to find out if any change in the degree of resistance occurred.

## *Method*

For testing the resistance sputum, sinus discharge or gastric contents were treated as follows. After elimination of the contaminants, using 3.46 per cent sulphuric acid for 35 minutes, an attempt was made to cultivate the organisms on media containing isoniazid in various concentrations, ranging from 0.02 microgram of isoniazid per cc. to 200 mcgm. per cc. At the beginning Youman's fluid medium was used, and later Loewenstein's egg medium. Every patient's sputum or sinus discharge or gastric content was examined six weekly, monthly, or if found necessary, even at shorter intervals. Every growth on the culture medium was tested microscopically to ensure that the colonies were of mycobacterium tuberculosis.

## *Results*

In all 56 patients were observed, but in 26 it was impossible to complete the investigation because 11 were discharged from the sanatorium, five died and 10 became negative on culture during the period of investigation. Of the remaining 30 patients 25 are resistant to isoniazid, some up to 200 mcgm./cc., and their resistance is steadily increasing from test to test.

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The remaining five of the 56 patients reversed their resistance. four of them gradually, and one abruptly.

Resistance of these five patients' bacilli regressed from about 1 to 6 mcgm. Isoniazid/cc. level of resistance to a normal sensitivity, the growth of the organisms being inhibited by 0.02 mcgm. Isoniazid/cc. Before this phenomenon is discussed, a brief summary of the patients' histories is presented.

*Case 1:* F.L. A 44 year old female, was admitted to Wooroloo Sanatorium in 1949, with 10 months' history of cough, sputum and huskiness of voice. On x-ray film a cavity 5 cm. in diameter was seen in the right upper lobe, with abundant spread to the lower part of the right lung and the left middle zone. On bed rest and streptomycin 1 gm. daily, an extensive increase in the disease in the left mid-zone appeared after one month, and para-aminosalicylic acid was added to the streptomycin treatment. On March 3, 1950 a marked improvement was noted on the x-ray film. On April 15, 1950 streptomycin and P.A.S. was ceased after three months' combined course. On June 16, 1950 the cavity in the right upper zone appeared larger, and continued to increase in size until, on March 5, 1951, Monaldi drainage was instituted with intracavitary instillation of 2 cc. P.A.S. solution twice daily, with marked diminution in the size of the cavity. Monaldi drainage was discontinued on April 30, 1951 and streptomycin and P.A.S. treatment recommenced. Just prior to right apicolysis with plombage, using lucite spheres, the cavity became larger and after operation a fresh spread to the left mid-zone was noted. On June 27, 1951 conteben treatment commenced. On January 21, 1952 right pneumonectomy was performed, followed by a broncho-pleural fistula and a widespread broncho-pneumonia on the left side. On June 17, 1952 all other chemotherapy was discontinued and isoniazid commenced. Improvement in her general condition occurred, the empyema space became smaller and the left lung partially cleared, in spite of the fact that the organisms grown on culture from her sputum and sinus discharge gradually became more resistant to isoniazid, finally reaching resistance to 6.0 micrograms per cc. Streptomycin and P.A.S. were added to the isoniazid on December 3, 1952 and by December 19, 1952 isoniazid resistance had fallen to the level of 0.24 micrograms per cc., and by January 16, 1953 her organisms were sensitive to isoniazid. In the x-ray film taken on February 4, 1953, clearing of the left lung was more marked. Throughout her sanatorium treatment she has been positive on direct smear or culture.

*Case 2:* D.D. A female of 47 years, was admitted to Wooroloo Sanatorium on February 22, 1948 with advanced bilateral pulmonary tuberculosis, with several cavities in the right upper lobe. She was treated conservatively on sanatorium regime until October 7, 1950, when P.A.S. was commenced. On March 12, 1952 conteben was added to the P.A.S. but no appreciable change in the x-ray films was noted. In July 1952 she appeared moribund, with gross oedema, ascites, and a markedly enlarged liver. She was taken off P.A.S. and conteben and given isoniazid. Her general condition improved dramatically, and on x-ray film some exudative lesions disappeared. Her sputum was positive on direct smear, and on September 26, 1952 the organisms were still sensitive to isoniazid. Subsequently, however, isoniazid resistance developed until December 19, 1952 when the organisms were resistant to 1 microgram per cc. of medium. On December 15, 1952 streptomycin and P.A.S. were added to the isoniazid, and by March 17, 1953 the large cavity in the right lung was reduced in size, the patient was comfortable and the quantity of sputum diminished, although remaining positive on direct smear. By January 30, 1953, however, the resistance of her organisms had decreased to a level of 0.24 micrograms per cc., and on February 20, 1953 they were isoniazid sensitive.

*Case 3:* M.S. A female patient of 45 years was admitted on October 19, 1952 with symptoms of some years duration. She had never consulted a doctor until her admission to the sanatorium. She presented as a case of far advanced bilateral pulmonary tuberculosis, with several cavities and with a wide bronchogenic spread. On admission she was in a desperate general condition. She was immediately given combined streptomycin and P.A.S. and isoniazid treatment. Her general condition during the last five months has improved considerably and x-ray films show regression of the exudative disease. She is still on combined chemotherapy. Her sputum was positive on direct smear on admission and remained so on culture until December 30, 1952, when she converted on ordinary Loewenstein culture, but two further sputa were positive on Loewenstein medium containing isoniazid on January 16 and January 31, 1953 (tests for isoniazid resistance). By November 21, 1952 her sputum contained organisms resistant to 0.06 micrograms per cc., and on December 19, 1952 the organisms were resistant to 6.0 micrograms per cc. On December 31, 1952 the level of resistance had fallen to 0.6 micrograms per cc., on January 16, 1953 to 0.24, on January 31, 1953 to 0.06, and on February 20, 1953 there was no growth on any culture medium.

*Case 4:* F.B. A male of 62 years was first admitted to the sanatorium on December 14, 1949 with one year's history of general lassitude, cough, sputum, loss of weight and appetite. He had a right upper lobe process with possible cavitation and he was treated on sanatorium regime. He absconded on September 24, 1950 and was re-admitted on December 30, 1950 with obvious cavitation in the right upper lobe. He started streptomycin and P.A.S. on March 13, 1952, but because of nausea and vomiting the P.A.S. was discontinued after one month and replaced by conteben. On August 12, 1952 he was taken off streptomycin and conteben and commenced on isoniazid. On February 4, 1953, in addition to isoniazid, streptomycin and P.A.S. were resumed, but on February 20, 1953, because of reaction, streptomycin was discontinued. Since 1949 his sputum has been consistently positive on direct smear or culture. His organisms became resistant to 0.6 micrograms of isoniazid per cc. of culture medium on September 26, 1952, six weeks after the institution of isoniazid and remained so until November 21, 1952. The cultures of December 19, 1952 and January 16, 1953 were contaminated, but on February 16, 1953 the organisms were again sensitive to all dilutions of the agent.

*Case 5:* S.K. A 60 year old male, was admitted to Wooroloo Sanatorium on November 28, 1951 with a four years' history of tuberculosis for which no active nor chemotherapeutic treatment had previously been given. He had had a recent large haemoptysis, and on admission his general condition was poor, with loss of energy, lassitude, cough, sputum and severe pain in the chest. His x-ray film showed atelectatic right upper lobe, with a large cavity in the middle zone and disease in the left lung. Streptomycin and P.A.S. were commenced and maintained until October 9, 1952, when they were replaced by isoniazid. On January 22, 1953 streptomycin and P.A.S. were added to the isoniazid. His sputum throughout treatment has been positive on direct smear. Resistance to 0.6 microgram of isoniazid per cc. of medium had developed by November 21, 1952, six weeks after the commencement of treatment, and by January 30, 1953 it had increased to the level of 1 microgram per cc. By February 19, 1953 his organisms were again isoniazid sensitive.

### *Discussion*

Some writers have demonstrated that streptomycin resistance of mycobacterium tuberculosis is not a constant property but may vary considerably without the institution of any other treatment. It has also been demonstrated that the combined use of chemotherapeutic agents diminishes

the likelihood of the appearance of resistant strains,<sup>1,2</sup> and further, that the continuation of treatment with the agent, against which the bacilli have already developed a certain degree of resistance<sup>5</sup> is not contra-indicated.

In some cases under observation in this survey, when isoniazid resistance developed, streptomycin and P.A.S. were re-introduced and led to fairly rapid disappearance of isoniazid resistant strains from their sputum, despite the fact that these drugs had not previously been effective in converting the sputum. Whether the reduction of the resistance level is permanent or temporary, requires further study and observation.

In three of the cases described above, the regression of the resistance is most probably related to the addition of streptomycin and P.A.S., in spite of the fact that Case 1 already presented a low degree of resistance against streptomycin, but was still sensitive to P.A.S.

In Case 2 it is obvious that streptomycin and P.A.S. treatment had a role in the reversion of the resistance to the normal level, a marked drop being noted six weeks after streptomycin and P.A.S. therapy was instituted; analysing this case the suggestion arises that the reversion of resistance may occur without the intervention of additional chemotherapy.

Case 3 is a bacteriological paradox; after one month of combined chemotherapy (streptomycin, P.A.S. and isoniazid) she developed isoniazid resistant organisms, the resistance increased to 6 micrograms isoniazid per cc. during the next four weeks and then gradually diminished, the organism finally becoming fully sensitive after four months of chemotherapy. In this case it is difficult to find a reasonable and acceptable explanation for the appearance and disappearance of the resistant strains. It is suggested that the abundance of organisms present initially, in the presence of gross caseous lobar and broncho-pneumonic disease, associated with the patient's apparently hopeless general condition, resulted in the rapid development of tolerance to the drug, although there was a gradual, progressive improvement in her clinical state.

The effect of streptomycin and P.A.S. is of course by no means instantaneous in the conversion of sputum, and another alternative is that these agents, to which in combination the development of resistance is a slow process, have in due course succeeded in eradicating the (isoniazid resistant) organisms from the sputum.

On culture tubes containing isoniazid (0.06 micrograms per cc. and 0.24 microgram per cc.) we obtained growth from the sputum, but the inoculum put up on ordinary Loewenstein medium on the same day did not show any growth. Unfortunately we were unaware at that time of the negative results of the routine sputum tests, and positive cultures from December 19, 1952 and January 16, 1953 were not retained. It is therefore not possible to prove that the strain of organism cultures was actually isoniazid dependent. If however, the existence of streptomycin dependent mycobacterium tuberculosis is accepted, it is not unreasonable to assume that isoniazid resistance will also develop.

In Case 4 it is difficult to draw any conclusion, because between No-

vember 1952 and February 1953 there were two series of contaminated culture tubes; streptomycin and P.A.S. were started on February 4, 1953 and by February 20, 1953 reversion of the resistance had occurred. We have to note that this patient from February 4, 1953 to February 20, 1953 had only 5 gms. of streptomycin. It is doubtful if such a quantity is able to have any influence on reversion of resistance.

In Case 5 the disappearance of the resistance more or less coincides with the beginning of the combined therapy, so that this may have had an important role in producing reversion of the resistance.

### Conclusions

In a review of patients who developed isoniazid resistant strains of mycobacterium tuberculosis during the last six months, five out of 56 patients were discovered in whose sputum resistant organisms again became sensitive to isoniazid. The disappearance of resistant strains occurred in most cases after commencement of additional streptomycin and P.A.S., but in one case the reversion could possibly have occurred without the assistance of these agents. In one case we noted the appearance of colonies in culture tubes containing isoniazid, when cultures of that patient were negative on normal Loewenstein medium. This fact is suggestive that in certain cases isoniazid dependent organisms may develop.

### SUMMARY

Isoniazid resistance of the mycobacterium tuberculosis is reversible *in vivo*, either by addition of other chemotherapeutic agents or possibly spontaneously. There is a suggestion of existence of isonicotinic acid hydrazide dependent mycobacterium tuberculosis.

### RESUMEN

La resistencia a la isoniácida al micobacterium tuberculosis es reversible *in vivo*, ya sea por el agregado de otros agentes quimioterápicos o posiblemente de manera espontánea. Hay una sugestión de que existe bacilo de Koch dependiente de hidracida del ácido isonicotínico.

### RESUME

La résistance du bacille de Koch à l'isoniazide est réversible *in vivo*, soit par l'addition d'un autre agent chimiothérapique, soit même spontanément.

On peut supposer qu'il existe des bacilles tuberculeux dépendants par rapport à l'isoniazide.

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# Effect of the Isoniazide on Guinea Pigs Infected with Isoniazide Resistant Strains of *Mycobacterium Tuberculosis*\*

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## *Introduction*

The task of our present investigation was to demonstrate the action of isoniazide, if any, upon the isoniazide resistant strains of mycobacterium tuberculosis. We endeavored to find the level of resistance beyond which the drug is no longer effective and no clinical improvement is to be expected.

It is a well known fact, that a relatively high percentage of patients, treated by isoniazid after the elapse of a certain period of time, or after a certain quantity of medication develop tubercle bacilli which are resistant to this drug.<sup>1-3</sup> We tried to demonstrate this fact by using guinea pigs as experimental animals.

## *Methods*

We had six groups of guinea pigs, each consisting of two individuals. The guinea pigs were approximately of the same age and weight (400 gms.). We infected all six groups with 0.1 mgm. of tubercle bacilli obtained from colonies grown on Loewenstein-Jensen medium. One of the strains was sensitive to isoniazide, the others were resistant for different strengths of isoniazide concentration. We considered the first group a control, the individuals of which were infected with isoniazide resistant strain (100 mcgm./cc.). The groups 2, 3, 4, 5, and 6 were infected with approximately the same quantity of mycobacterium tuberculosis, but of different degrees of resistance.

The individuals of the second group were injected with a strain cultured from sputum of a patient who had never been treated with any anti-tuberculous chemotherapeutic agent and whose bacilli had been proved sensitive to isoniazide, i.e. it had not been possible to subculture them in presence of isoniazide in concentration of 0.02 mcgm./cc. The third group was inoculated with micro-organisms resistant to isoniazide in concentration of 0.1 mcgm./cc. The fourth group was infected with a strain resistant to 1 mcgm./cc., the fifth group received injection with bacilli resistant to 20 mcgm./cc. and the sixth group was infected with mycobacterium tuberculosis resistant to isoniazide up to the concentration of 100 mcgm./cc.

The infected guinea pigs were injected subcutaneously in the right inner thigh on the same day, with approximately the same quantity of micro-organisms and kept in separate cages from the moment of inoculation.

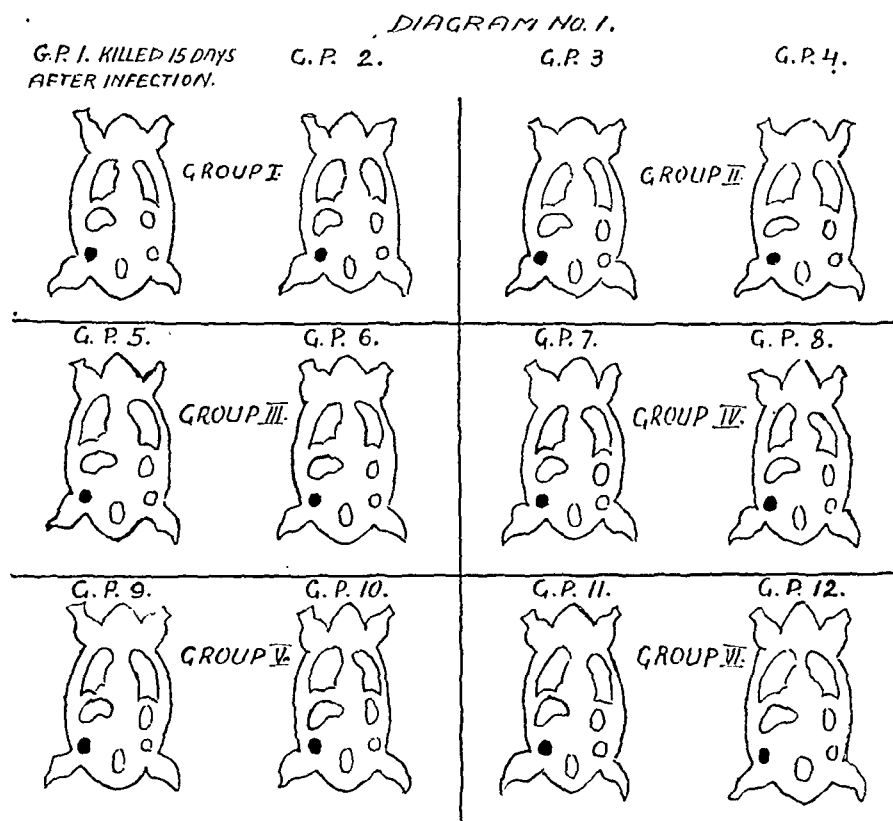
\*From the Woorloo Sanatorium, Wooroloo, W. Australia. Medical Director, H. R. Elphick.

\*\*Presently at Onondaga Sanatorium, Syracuse, New York.

We provided them with similar food and living conditions. Their food consisted daily of 1 oz. of dry food with the following composition: 10 per cent whole wheat, 40 per cent bran, 40 per cent crushed wheat, 5 per cent meat meal,  $2\frac{1}{2}$  per cent bone meal,  $2\frac{1}{2}$  per cent buttermilk, for every kilogram weight of dry food one teaspoonful of common salt was added. For green food and water we gave them lettuce and carrots, the quantity varied with the temperature of the air and the animals demand.

The first group served as controls and was not treated, but one of the two guinea pigs were killed on the 15th day after inoculation, to verify the progress of the infection. The other animals were examined clinically (see diagram No. 1) and we found that everyone had lymph node involvement and the animals already presented general symptoms, consisting of loss of weight and diminished appetite. The sacrificed guinea pig (first group) presented major caseation and enlargement of right inguinal lymph nodes and an enlarged para-lumbar lymph node. From the caseous lymph node we were able to demonstrate acid fast bacilli, whose size, shape and staining behavior were characteristic of mycobacterium tuberculosis.

Beginning with the 15th day, the animals of the 2-6 groups were given isoniazide, with a dose of 4.4 mgm. per kilogram of bodyweight for 10 days, after which the dosage was increased to 6 mgm. per kilogram. Fifty per cent of the drug was given orally mixed with dry food and 50 per cent by daily hypodermic injections.



### Results

In three to four days from the beginning of treatment we noticed that the appetite of the animals in the treated groups improved considerably, so that we had to increase the quantity of dry food to one and one-half ounces per day.

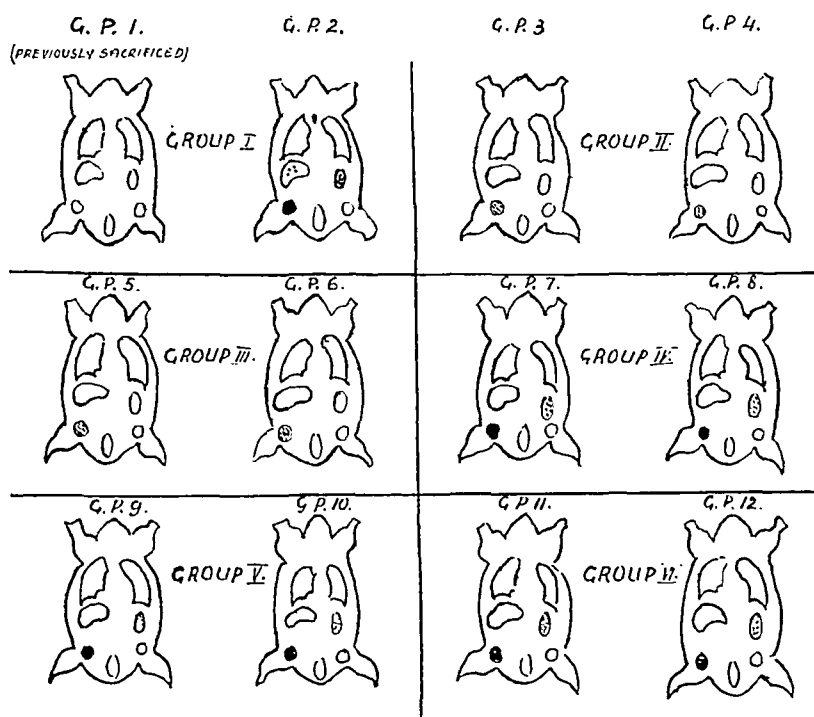
On the 15th day we examined the animals, but no significant change was found in the clinical picture, except that the treated animals ceased to lose weight.

After six weeks of treatment the animals were killed and examined. The results of examination are summarized diagrammatically in diagram No. 2.

According to diagram 2, the treatment was successful up to group 3. If we compare the pathological alterations in groups 4, 5, and 6 with the alterations of group 1 we still find that a certain difference exists between these groups. The spread of the disease in the treated groups (4, 5, 6) is not as advanced as in the untreated group 1.

The lymph nodes of the guinea pigs were examined microscopically in an endeavor to demonstrate the difference, if any, in the various groups, but no essential difference was demonstrable, between the treated and non-treated groups.

DIAGRAM NO 2.



### *Discussion*

It has been demonstrated by various writers, that patients treated by streptomycin after a lapse of time develop streptomycin resistant organisms. If the resistance reaches the level of 50 to 100 mcgm./cc. and the patients are further treated with the same antibiotic, it fails to improve the condition of the patients. On the other hand the survival of the guinea pigs infected by streptomycin resistant organisms treated by streptomycin and the untreated control groups did not show any marked difference.<sup>4-6</sup> Other writers demonstrate that some clinical improvement could be achieved most probably owing to the fact that an increased acquired resistance occurs as a consequence of the destruction of the still sensitive strains.<sup>8</sup> As we demonstrated above, the animals infected with organisms resistant to 1 mcgm. isoniazide/cc. or with micro-organisms with higher resistance than that do not respond markedly to the treatment with isoniazide or in any case not in such degree to justify the continuation of the treatment. For instance in group 2 during the treatment a generalization of the tuberculosis did not occur, the process was localized to the regional lymphatic nodes, macroscopically a certain regression was noted. On the other hand in groups 4, 5, and 6 an involvement of the spleen was evident as a sign of generalization of the tuberculous process.

Knowing that the type of tuberculosis developing in the guinea pig differs from that in the human, so the problem arises that the above statement which applies to the guinea pig may not be applicable to human tuberculosis, which develops on a substratum with a certain inborn and acquired resistance. This is a matter which has to be considered and requires further careful study and observation.

If the therapy were maintained for a longer period the difference between the groups might be more marked and further improvement could occur in the treated groups. These problems are under current investigation in this laboratory.

### SUMMARY

Isoniazide administered for six weeks in the treatment of tuberculosis of the guinea pig infected with isoniazide resistant mycobacterium tuberculosis is effective to the resistance level of 1 mcgm./cc. Above this degree of resistance the progress of the disease is delayed in comparison with the non-treated control animals.

### RESUMEN

La isoniácida administrada por seis semanas en el tratamiento de la tuberculosis en cuyos infectados con microbacterias tuberculosis resistentes a la isoniácida, es efectiva a una concentración de 1 mcgm./cc. Sobre este grado de resistencia la evolución de la enfermedad es retardada en comparación con la observada en los animales de control no tratados.

### RESUME

Chez les cobayes inoculés avec des bacilles tuberculeux résistants à l'isoniazide, l'action du traitement par ce produit administré pendant six

semaines reste efficace lorsque le taux de résistance ne dépasse pas un gamma par cc. Au-dessus de ce degré de résistance, l'évolution de l'affection est simplement prolongée par rapport à celle des animaux témoins non traités.

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# A Study on Therapeutic Evaluation of Isoniazid in Treatment of Pulmonary Tuberculosis

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Clinical studies of the hydrazid derivatives of Isonicotinic Acid were initiated at Eastern North Carolina Sanatorium on April 5, 1952. This investigation was directed toward therapeutic evaluation and toxic effects of this drug.

## Materials

Ninety-two patients were studied. Almost all had extensive, active, pulmonary tuberculosis. Many of them had previously been given one or more of the currently accepted treatments and all patients had positive sputum.

Classification of the pulmonary status and other details of the pre-study period of these patients are to be found in Table I.

TABLE I

	Number of Cases
Total Number of Cases	92
Male	60
Female	32

## Race, Age

White	61
Colored	31
Average age	45.7

## Classification of Their Pulmonary Tuberculosis

Far advanced	71 - 77%
Moderately advanced	20 - 21%
Minimal	1 - 1%

## Previous Duration of Disease

6 months	20
6 to 12 months	19
1 to 2 years	31
2 years and more	22

Isoniazid has been given to two patients for 11 months, to 82 for nine months, and to eight for five months (Table II).

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TABLE II

*Type of INAH Therapy*

Type	Number of Cases
Cases Given INAH Alone.....	29
Cases Having Had No Other Drug..	6
Cases Given INAH and Streptomycin .....	9
Cases Given INAH, Streptomycin, and PAS.....	54

<i>Duration of INAH Therapy</i>	
Cases Given INAH for 11 Months .....	2
Cases Given INAH for 10 Months.....	82
Cases Given INAH for 5 Months .....	8

Most of the patients are still on isoniazid. The dose was standardized at three to four milligrams per kilogram. It was given twice daily, one dose in the morning before breakfast, the other at bed time.

In the group treated with dihydrostreptomycin, isoniazid and PAS combined, almost all patients (except the two with miliary disease and the two with meningitis received one gram of streptomycin twice a week and 12 grams of PAS daily.

*Results*

A) *On General Condition:* Since the great majority (77 per cent) of the cases were far advanced, the first result of therapy was seen on general condition and clinical signs. Toxic systemic manifestations such as temperature elevation, asthenia, anorexia, weight loss, and malaise, showed in general significant amelioration within two or three weeks after isoniazid was started. Likewise, there was less sputum and cough, increase in appetite, gain in weight, and a feeling of well being.

In 17 of the 92 cases (19 per cent) marked improvement was noted. In 40 (43 per cent) slight symptomatic improvement was noted. Eight (8 per cent) showed slight temporary improvement. In 21 (23 per cent) the general condition was unchanged and six cases (6 per cent) became worse while on therapy (Table III).

TABLE III: RESULTS OF ISONIAZID TREATMENT

<i>A. General Condition</i>		Number of Cases
Condition		
Markedly Improved .....		17
Improved .....		40
Temporarily Improved, Then Relapsed ..		8
Unchanged .....		21
Worse .....		6

<i>B. Sputum</i>		Number of Cases
Negative at Administration of Drug ..		11
Converted to Negative in Smear .....		12
Temporarily Negative in Smear .....		18
Remained Positive .....		51



The first two patients were put on isoniazid at the beginning of April 1952. They were not told what they were being given, thereby eliminating any psychological effect of receiving the drug. Both of these patients were in a toxic condition, having far advanced, extensive, bilateral disease. Within three weeks an almost dramatic amelioration began.

Eighty-two were placed on isoniazid on May 6, 1952. In the great majority of this group (65 cases) improvement (moderate and mild) has been observed. It is interesting to note that six of them showed significant prompt and temporary elevation of temperature for the first five or six days (Table VI) and then experienced a decline in temperature which remained normal with continuation of therapy.

The group showing temporary improvement (eight cases) and many of the others showed late recurrence of fever and other symptoms of tuberculosis after an average of five or six months period of therapy (Table III). Defervescence was accompanied by an equally rapid reverse of toxic manifestation. On the other hand recurrence, also, was accompanied by parallel, progressively increasing toxic manifestation of tuberculosis. This was explained as a possible development of resistance; in other words, multiplication of non-sensitive microbacteria. Signs of improvement such as a sense of well being, improved appetite, return of strength and energy, were the earliest results of isoniazid therapy. Weight gain followed in about three or four weeks of treatment. Among this group of 65 maximum weight gain was 38 pounds, minimum weight gain was eight pounds, and the average was 12 pounds.

B) *Effect on Cough and Sputum*: Significant decrease in cough and in amount of sputum has been noticed. In 12 (13 per cent) the sputum became negative on smear; only three were negative by culture. In 11 previously positive, sputum was negative at the beginning of drug administration.

In 18 (19 per cent) sputum smears became negative temporarily. In the great majority (51 cases or 55 per cent) sputum smears remained positive, although a decreased count was reported (Table III).

C) *X-ray Changes*: Obviously x-ray film observations were made in all cases. Periodic films did not reveal changes comparable to those observed in the general condition of the patients. Complete x-ray film clearing was not seen in our series. Twenty-three (25 per cent) showed slight improvement. Seventeen (18 per cent) were markedly improved. In only two did a cavity disappear and 32 (35 per cent) were unchanged. On the other hand 10 patients changed for the worse. Of the 17 cases showing marked improvement, 10 (58 per cent) were given combined therapy consisting of streptomycin, para-aminosalicylic acid, and INAH. Many cases in the group showing slight improvement became worse within five to six months after administration of isoniazid, even though their general condition continued to improve. Of the 17 mentioned above as markedly improved, one with bilateral cavitation and with bacilli resistant to dihydrostreptomycin showed the cavity on one side closed, and it was possible to do lobectomy on the opposite side. This patient's tuberculosis remains stable

six months after surgery in spite of the fact that isoniazid was discontinued immediately after the operation because of suspected toxicity which will be mentioned later. In another case, acutely ill with extensive, exudative infiltration in the right upper and left lower lobes, isoniazid was given alone. Marked improvement took place, both radiologically and clinically, for the first eight months; but after that the sputum, which had become negative for a short time, again became positive and there was no further x-ray film change. In the third case a cavity disappeared roentgenologically (Table IV).

TABLE IV: X-RAY CHANGES

Type of Therapy	Total No. of Cases	Improved No. Pct.	Markedly Improved No. Pct.	Cavity Gone No. Pct.
INAH Alone	29	9 (31)	5 (17)	2 (6)
INAH & Strept.	9	4 (48)	2 (23)	
INAH, Strept. & PAS	53	10 (18)	10 (18)	

TABLE IV (Continued)

Type of Therapy	Total No. of Cases	Unchanged No. Pct.	Worse No. Pct.
INAH Alone	29	10 (34)	4 (13)
INAH & Strept.	9	3 (33)	
INAH, Strept. & PAS	53	27 (50)	6 (11)

On the other hand, in four cases new cavities appeared. In three enlargement of old cavities occurred. In two the appearance of new exudative disease occurred during isoniazid treatment.

D) *Extra-Pulmonary Tuberculosis* (six cases): These cases, so classified, all had some degree of pulmonary tuberculosis in addition. In two cases of tuberculous meningitis, one of empyema, and one of bronchopleural fistula, isoniazid has been used with streptomycin and para-aminosalicylic acid. The one with bronchopleural fistula and empyema improved and lobectomy was done on that side. Good results were also noted in one case of tuberculous orchitis and in one of tuberculous fistula-in-ano (Table V).

TABLE V: EXTRA-PULMONARY TUBERCULOSIS

Diagnosis	Number of Cases
Tuberculous Meningitis	2
Tuberculous Empyema	1
Bronchopleural Fistula and Empyema	1
Orchitis	1
Fistula-in-ano	1

*Toxicity*

In cases receiving isoniazid, the cephalin flocculation test has been used for liver function; and urine, blood and sputum examinations have been done routinely. All systems were watched closely for signs of intoxication. Some toxic effects have been noted (Table VI). For instance, in one case which showed satisfactory roentgenological results, bilateral peroneal palsy

TABLE VI: DRUG TOXICITY

Toxic Manifestations	No. of Cases	Drug Discontinued	Drug Continued
Persistent Liver Function Disturbance. 4+* Cephalin Flocculation Test	4	4	
Micturition	2	1	1
Bilateral Peroneal Palsy	1	1	
Peripheral Neuritis (in both legs)	1		1
Urticaria	1	1	
Hyperleukocytosis	6		6
Mental Depression	6	4	2
Suicide	1	1	
Attempted Suicide	1		1
Elevation of Temperature	6		6
TOTAL	29	12	17

with muscular atrophy occurred immediately after excisional surgery. It is true that this individual is neurotic but he has developed an organic neurological complication. In this case general anesthesia can be suspected of having precipitated the toxic side effect of the drug. In another case, also, similar trouble was seen right after surgery, but it was neither as severe nor as permanent. One case given isoniazid prior to surgery developed paranoid obsessions right after surgery and continued for approximately two months. Also, in this case surgical shock or general anesthesia can be suspected.

Six developed mental depression, one of whom committed suicide. A second attempted suicide, and two of the others had a complete depressive psychosis, e.g. symptoms abated when drug was discontinued and returned upon giving the drug again. In four other cases some personality changes occurred. They became almost childish, un-cooperative. In two cases difficult micturition has been seen.

Other toxic symptoms appeared as follows:

In six cases temporary initial rise in temperature; in six leukocytosis (between 20,000 - 25,000); in one urticaria developed; in four cephalin flocculation test was 4+, and, because of this, drug administration was discontinued. Urine tests showed no change and no failing kidney function.

In five antihistaminic drugs were given during isoniazid therapy and in

none of them was there evidence of incompatibility. Administration of prostigmine bromide did not relieve difficult micturition in the two cases in which it was tried.

In a great majority of cases side effects due to drug toxicity appeared early in the course of treatment, almost all by the third or fourth week. In some cases toxic symptoms cleared after the drug was stopped, and did not reappear when it was started again; but in others the opposite was true.

#### *Results from Drug Combinations*

Twenty-nine of the 92 cases were given isoniazid alone. Six of them had had no previous chemotherapy. Nine of the 92 were given isoniazid plus streptomycin. Fifty-four of the 92 were given all three drugs, i.e. streptomycin, isoniazid, and PAS (Table II). The cases given isoniazid and streptomycin showed the highest percentage of x-ray improvement, nine of these in all; four of them (48 per cent) showed slight to moderate improvement, and two (23 per cent) marked improvement in x-ray film and general condition.

#### *Comment*

Even though a number of studies have been published, it is thought that more knowledge and more experience coming from several and different sources is needed on this subject. Also, we believe that every investigator should continue to publish his own experiences until we can get a much more crystallized opinion. In the past 10 years great advancement in the treatment of tuberculosis has taken place, both medical and surgical. Changes have occurred rapidly; but more investigations, more observations, and more time will be required before the underlying realities can be finally determined.

This clinical study reveals isoniazid as another useful weapon in the treatment of tuberculosis, but not the final answer. In other words, the result of this investigation has not proved that isoniazid can sterilize host organisms from acid-fast bacilli. Even in the dose of three to four milligrams per kilo used in this series of cases, certain significant toxic side effects occurred. Sensitivity studies were not available, but the clinical course, x-ray film examinations, and sputum studies have given the impression that resistance to isoniazid may develop within five to six months.

Early clinical effect has been seen in amelioration of the systemic toxic reactions so common in tuberculosis. Then improvement of respiratory symptoms was observed. X-ray film clearing was not as satisfactory as was the symptomatic improvement. The number of bacilli was reduced in the sputum smears temporarily and in some cases remain negative, this in 13 per cent of the cases. In the others the bacillary count was often reduced at least temporarily and some were negative for periods of two to three months only to become positive again.

Isoniazid offers new hope for all tuberculous patients, but especially for streptomycin resistant ones in need of further medical or surgical treatment. It is relatively inexpensive. There is also the advantage of being able to give it orally without causing a serious gastrointestinal disturbance.

General experience recommends using isoniazid in connection with another anti-tuberculosis drug, to prevent early resistance.

The toxicity of isoniazid is a problem, in some cases indicates discontinuation (12 out of 92). Serious central nervous system side effects are more common in persons who have unstable personality or history of previous psychotic episodes or previous convulsive disorders. Toxic side effects have been seen in other systems of the body, but they were not so serious.

### SUMMARY

Isoniazid has been given to 92 cases in the Eastern North Carolina Sanatorium starting April 4, 1952, for a five to 11 months period. The great majority had received streptomycin and PAS previously. These investigations were directed toward the evaluation of therapeutic and toxic effects of the drug.

Because the great majority of the studied cases (77 per cent) were far advanced, the first results of therapy were seen on the general condition. Relief of the common toxic symptoms of tuberculosis occurred early. Specific respiratory symptoms were slower. Systemic toxic manifestations of tuberculosis ameliorated almost dramatically within three to four weeks. In the following phase respiratory signs were diminished. X-ray film changes were not as significant as was the clinical improvement.

Clinical, and in some cases roentgenological, improvement gradually increased for about five or six months, after which there was either no further change or there was evidence of relapse.

Toxicity of the drug, especially on the central and peripheral nervous systems, is reported.

### RESUMEN

Se ha usado isoniácida en 92 casos en el Sanatorio del Noreste de Carolina del Norte, empezando en Abril 4 de 1952 y por 5 a 11 meses de duración. La gran mayoría habían recibido estreptomicina y PAS antes. Estas investigaciones se orientaron hacia la valuación de los efectos terapéuticos y tóxicos de la droga.

Como la mayoría de los casos estudiados (77 por ciento) eran muy avanzados, los primeros resultados fueron observados en el estado general. Pronto ocurrió el alivio de síntomas tóxicos comunes.

Más lentamente mejoraron los síntomas respiratorios propios de la tuberculosis. Las manifestaciones tóxicas generales mejoraron casi dramáticamente dentro de tres a cuatro semanas. En la fase siguiente los signos respiratorios disminuyeron. Los cambios radiológicos no fueron tan significantes como los clínicos.

La mejoría clínica y en algunos casos la radiológica aumentó gradualmente por 5 o 6 meses aproximadamente después de los cuales ya no hubo cambio o hubo recaída.

La toxicidad de la droga especialmente sobre los sistemas nerviosos central y periférico, se refiere.

## RESUME

L'isoniazide a été donnée à 92 malades dans le Sanatorium de la Caroline du Nord-Est, à partir du 4 avril 1952 pendant une période de 5 à 11 mois. Dans la grande majorité, les malades avaient reçus antérieurement streptomycine et P.A.S. Les investigations eurent pour objet l'évaluation de l'effet thérapeutique et toxique de la drogue.

Etant donné que la grande majorité des cas étudiés (77%) étaient des formes de tuberculose très avancées, les premiers résultats du traitement portèrent sur l'état général. Précocément on assista à l'amélioration des symptômes généraux d'intoxication de la tuberculose. L'action portant véritablement sur l'arbre respiratoire fut plus lente. Les manifestations toxiques de la tuberculose s'améliorèrent d'une façon quasi théatrale, en trois ou quatre semaines. Dans un stade ultérieur, les troubles respiratoires diminuèrent. Les modifications radiologiques ne se montrèrent pas aussi nette que les améliorations cliniques.

Les symptômes cliniques et dans certains cas radiologiques s'améliorèrent graduellement pendant cinq ou six mois environ. Au bout de ce temps, il n'y eut plus d'amélioration ou il y eut au contraire apparition de rechutes.

L'auteur fait état de l'action toxique du produit, spécialement sur le système nerveux central et périphérique.

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# The Treatment of Tuberculous Meningitis in Infants with Streptomycin and Isonicotinic Acid Hydrazide (Isoniazid)\*

A Preliminary Report of Six Patients Under the Age of Two Years  
Treated Without Intrathecal Medication.

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The addition of streptomycin to the therapeutic regimen has changed the natural history of tuberculous meningitis in both adults and children. This has been amply demonstrated in the case of children in the large series of patients treated by workers both here and abroad using streptomycin intramuscularly and intrathecally, usually in combination with a sulfone derivative. The universally fatal mortality of this disease has been markedly and significantly reduced by this method.<sup>1-4,26,29,33</sup>

Despite these accomplishments, there is still a great need for improvement of therapeutic results in tuberculous meningitis. The number of fatalities, and the degree and number of significant neurological residua, have made it incumbent upon the clinician to seek newer therapeutic agents or, at least, new combinations of existing anti-tuberculous agents. Furthermore, there are certain disadvantages to the use of streptomycin intrathecally. This method of medication is a cumbersome one, trying to the patient and the physician. It results in the introduction into the sub-arachnoid space of an irritating substance which may give rise to pleocytosis, fever, and convulsions,<sup>5</sup> confusing the clinical picture and temporarily increasing the degree of illness of the patient.

The preliminary studies of isoniazid *in vitro*<sup>6,7</sup> in animal experiments,<sup>6-10</sup> and in early clinical trials<sup>10-13</sup> indicate that it has an anti-tuberculous action of significant proportions. It has exhibited only minor toxicity and a low degree of pharmacodynamic side effects in animals and humans.<sup>13-16</sup> Its high degree of diffusibility makes it particularly useful where a high concentration of chemotherapeutic agents is required, particularly in body fluids. It has the property, unique in anti-tuberculous agents, of exerting a bacteriostatic effect on intracellular tubercle bacilli.<sup>17</sup> It was early demonstrated that the isoniazid molecule appeared in significant concentration in the cerebrospinal fluid.<sup>16</sup> It appears likely also, that the combination of this drug with streptomycin may forestall the emergence of isoniazid and/or streptomycin resistant strains of tubercle bacilli.<sup>18,19</sup>

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The Isoniazid used in this study was supplied by Merck & Company, of Rahway, New Jersey; C. Pfizer & Company, Brooklyn, New York, and Schering Corporation of Bloomfield, New Jersey. Sodium salt of PAS was supplied by Merck & Company of Rahway, New Jersey, and the Panray Corporation of New York City.

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Moreover, the recent work of Mackaness and Smith<sup>32</sup> presents rather definite evidence both in vivo and in macrophage cultures that the combined use of streptomycin and isoniazid may result in an acceleration of the death rate of intracellular and extracellular tubercle bacilli.

All of these properties of isoniazid make it particularly suitable for trial as an adjuvant agent in the treatment of tuberculous meningitis, both as a means of circumventing the use of intrathecal medication and also as a means of increasing the bacteriostatic effect of streptomycin.

Both in Europe and America, there have already appeared encouraging preliminary clinical evaluations of the effects of these agents, either alone or in combination with streptomycin in the treatment of tuberculous meningitis. The number of cases has been small, the periods of observation short and the age distribution of the patients variable. Klee<sup>13</sup> employed intrathecal isoniazid with beneficial results. Ragazzini and his colleagues<sup>20</sup> made use of isoniazid intrathecally in association with streptomycin and a sulfone. Sweetman and Murphy<sup>21</sup> treated one case with isoniazid alone with good results, and three with isoniazid following intramuscular and intrathecal streptomycin with equivocal results. All felt that results were sufficiently striking to justify further trial with these drugs.

Clark, et al.,<sup>22</sup> also report a favorable effect on tuberculous meningitis treated with isoniazid when used in combination with streptomycin, intramuscularly and intrathecally. They report on two cases treated with streptomycin and isoniazid without streptomycin intrathecally with encouraging results. Three of 10 treated with isoniazid alone died, in the first week of treatment. It was their feeling that isoniazid alone was not sufficient in the treatment of tuberculous meningitis but that its use with streptomycin might obviate the use of intrathecal therapy.

This present report is concerned with a preliminary evaluation of our experience with the treatment of tuberculous meningitis in six children under the age of two years. All have been treated from the outset, except the first case, with streptomycin intramuscularly and isoniazid by mouth or intramuscularly without the intrathecal use of either streptomycin or isoniazid. Their clinical and spinal fluid response was sufficiently impressive to make their reporting seem worthwhile as a preliminary indication that streptomycin and isoniazid when used in combination, may give results comparable to those obtained with the use of intrathecal and intramuscular streptomycin and promizole without the disadvantages of intrathecal therapy.

#### *Material and Methods*

This group consists of six children ill with meningeal tuberculosis, five females and one male, five white and one Negro, ranging in age from seven to 21 months. Diagnosis in each case was based upon: (1) history of exposure to a known case of pulmonary tuberculosis in the household; (2) positive tuberculin test,—in several cases following a previously negative test; (3) characteristic cerebrospinal fluid findings; (4) recovery of tubercle bacilli from the spinal fluid in three of the six and (5) x-ray film



evidence of pulmonary tuberculosis in all, two of them miliary. All had received some intramuscular streptomycin before admission. These courses were usually short and associated with interrupted use of PAS. Only one, D.M., had received streptomycin intrathecally totaling 10 injections of 50 mg. each. None had received isoniazid. All had shown progression of disease without response to therapy prior to admission.

### *Therapeutic Regimen and Scheme of Management*

#### *I. Streptomycin:*

Streptomycin sulfate was given intramuscularly in a dose of 0.5 grams per day, irrespective of body weight until the spinal fluid had been normal for three months. Thereafter it was given in dosage of 0.5 gram three times a week.

#### *II. Isoniazid:*

In the first patient (D.M.) the dose of isoniazid was begun at 4 mg. per kilo and increased within a period of 10 days to 10 mg. per kilo. All others received from the beginning a daily dosage of 10 mg. per kilo. Whenever tolerated, this was given orally, mixed with solid or pureed food, and divided in three or four doses in 24 hours. Vomiting was common early in the course of treatment and when this occurred, intramuscular isoniazid (Cotinazin, Pfizer) was given also in divided doses. If vomiting occurred within one hour after an oral dose, an equivalent dose was repeated intramuscularly.

#### *III. PAS:*

This was given as the sodium salt mixed with pureed foods in divided doses for a total daily amount usually of 2 grams. PAS had often to be discontinued because of gastro-intestinal irritation and frequently the dose was cut in half or discontinued entirely for considerable periods of time to avoid serious fluid and electrolyte disturbances. PAS was re-instituted in those who could tolerate it, particularly during the period of convalescence. Two patients who could not tolerate PAS were put on promizole.

#### *IV. General Measures:*

Energetic nursing care, and special attention to nutrition were deemed to be of great importance. Feeding by intermittent gavage had often to be resorted to in the early stages of treatment. Dietary supplementation with high protein materials and vitamins was employed. In the early acute phase, careful attention to sedation was necessary. Tub baths were useful for sedation and muscular relaxation and to combat episodes of extreme hyper-pyrexia. The use of suction in maintaining an airway free of tracheo-bronchial secretions and the use of oxygen were often needed. Early attempts at muscular re-education were undertaken to prevent deformities associated with sustained muscular contractions.

### *Laboratory Data Used in Follow-up*

#### *A. Spinal fluid:*

Spinal fluid examinations for cells, protein, and sugar were done weekly during the early course of treatment, but once the favorable direction of

clinical progress was determined, the number of spinal taps was reduced to one or two a month. Chlorides were determined only infrequently since our experience corresponded to that of Lincoln<sup>23</sup> in that this measurement was not found to be useful in following the course of the disease. Two consecutive spinal fluids were examined by smear and culture for tubercle bacilli before the initiation of therapy in each case. During the early months of therapy, cultures of spinal fluid for tubercle bacilli were done on frequent occasions. The number of these determinations also was diminished as the patient showed clinical improvement, since tubercle bacilli were obtained in only one case after the first month of therapy. Serial determinations of the plasma and spinal fluid levels of streptomycin and isoniazid, were performed in all at varying periods after an oral or intramuscular dose. Streptomycin levels were determined by the method of Stebbins and Robinson<sup>24</sup> and isoniazid levels by the method of Kelly and Poet.<sup>25</sup>

B. Complete urinalysis was performed once a week.

C. Complete blood and differential white counts were done twice a month.

D. Thymol turbidity, cephalin flocculation, and icteric index determinations were performed every two weeks during the course of therapy. Blood urea nitrogen was determined every three weeks.

E. Roentgenograms of the chest were obtained every two months.

F. Electrocardiograms were obtained at the beginning of therapy and repeated after three to six months of treatment.

### *Results*

#### *A. Clinical Responses:*

These children have been under continuous treatment with the above outlined regimen for periods ranging from four to 13 months. Their clinical and cerebrospinal fluid response is summarized in Table I. At present, all are alive and have shown distinct improvement.

The responses in general clinical state and in signs of meningeal irritation were gradual but striking in all. No dramatic immediate responses were noted but in every case beginning usually within two weeks after the initiation of therapy, there was gradual diminution in muscular rigidity, improvement in the state of consciousness and complete cessation of convulsive seizures. Signs of meningeal irritation disappeared within two to four months after the beginning of treatment. In no case was there progression of the focal neurological signs or of the cerebral irritative phenomena after the start of treatment. In one case, P. S., after four months there occurred a complete left facial palsy. This slowly and almost completely disappeared after physiotherapy and continued treatment of the meningeal process.

Their general nutritional state followed improvement in the neurological sphere. There were none of the manifestations of voracious appetite such as have been reported in the isoniazid therapy of pulmonary tuberculosis in adults,<sup>10,11</sup> nor have there been any dramatic changes in weight. Weight

TABLE I: Summary of Clinical and CSF Findings in Six Cases of Tuberculous Meningitis Treated with Streptomycin and INAH Without Intrathecal Medication

Patient	Mos. of Observ. Under Rx., INAH and SM.	Previous Rx. Before Start of Combined Therapy	Clinical State At Start of SM and INAH Rx.	--- SPINAL FLUID ---					Clinical State at End of Observation Period
				Before Therapy Cells	Proteins	Sugar	Observation Period Cells	Proteins Sugar	
D.M. Male 16 mos.	13	3 wks. SM 0/5 G.I.M./day 50 mg. I.T. for 10 days	Comatose, status epilepticus; im- paired of sight & hearing; hyper- pyrexia; lt. abdu- cens paralysis; dehydrated; mal- nourished; cyano- tic; bilat. papill- edema.	285	285	26	1	27 55	Clinical state excellent no focal or meningitic signs; hearing and sight seriously impaired but improved; mentally retarded; ataxic, unable to sit alone; afebrile 11 mos.; CSF normal 8 mos.
P.S. Female 16 mos.	11	DSM 0/5 G.O.D., IM for 3 wks.; no I.T. Rx.	Semi-comatose, generalized convul- sions; impairment of sight and hearing; bilat. internal strab- ismus; bilat. pap- illedema, malnu- trition; dehydra- tion; gen. spasti- city of limbs.	52	81	10	2	29 53	Clinical state excellent, no focal or meningitic signs; hearing and sight improved but still impaired; slight hydrocephalus since admis- sion; mentally retarded; unable to sit alone; left facial palsy at 4½ mos. almost dis- appeared; scoliosis of spine evident at 6 mos. improved; afebrile 8½ mos.; CSF normal 8½ mos.
J.S. Female 7 mos.	10	DSM 0/5 G BID for 7 days; no I.T. Rx.	Associated military tuberc.; no focal or meningitic signs; febrile dehydrated; malnourished; cy- anotic.	10 11	43 53	41 40	0	30 42	Clinical state excellent, no neurological abnormalities; all activities normal; afebrile 8 mos.; CSF normal 6½ mos.
SM—Streptomycin. DSM—Dihydrostreptomycin.			IT—Intrathecal. IM—Intramuscular.	Tubercle Bacilli isolated on admission					CSF—Cerebrospinal fluid. INAH—Isonicotinic Acid Hydrazide.

## TUBERCULOUS MENINGITIS IN INFANTS

TABLE I (Continued)

Patient	INAH and SM.	Before Start of Combined Therapy	Clinical State At Start of SM and INAH Rx.	--- SPINAL FLUID ---				Clinical State at End of Observation Period	
				Before Therapy	At End of Observation Period	Sugar	Proteins		
L.L. Female 11 mos.	7½	SM 0/25 G 3 doses; no I.T. therapy	Semi-comatose; focal seizures; left abducens paralysis; gen. spasticity of limbs; impairment of sight and hear- ing; bilat. papill- edema; mal- nourished.	250	2	140	57	52	Clinical state and nutrition excellent; no meningitic signs; abducens paralysis and strabismus less marked; anisocoria present; vision greatly improved; hearing normal; afebrile 6½ mos.
M.F. Female 21 mos.	6½	SM 0/4 G per day for 1 mo.; no I.T. Rx.	Comatose; sustained opisthotonus and extreme rigidity of extremities; lt. abducens paralysis; ptosis lt.; lt. facial paresis; bilat. papilledema; slight hydrocephalus.	27	4	94	22	54	Tubercle bacilli isolated on admission
D.P. Female Negro	4	SM 0/3 G per day for 21 days; DSM 0/3 G per day for 10 days	Hyperexia; no meningeal signs. Positive tuberculin test. Miliary and tracheobronchial lymph node tuberc. Nutrition fairly good.	104	3	64	26	48	Tubercle bacilli isolated on admission
SM—Streptomycin. DSM—Dihydrostreptomycin.				IT—Intrathecal. IM—Intramuscular.				CSF—Cerebrospinal fluid. INAH—Isonicotinic Acid Hydrazide.	

gains have been gradual, and steady and between three and five months of therapy were required before their standard weight was attained. There were temporary setbacks in the weight pattern which were ascribed to frequent vomiting as the result of PAS administration, but when the dosage of this medication was reduced or excluded as soon as vomiting occurred, weight gains continued to rise progressively.

Careful clinical observations were made on the progress of focal neurological lesions. The extra-ocular muscle imbalance in the patients treated for a longer period (as D.M. and P.S.) has disappeared completely and required between four and six months of therapy to do so. Extra-ocular muscle imbalance in the cases of L.L. and M.F. has greatly diminished since admission but is still present. Examinations of the auditory and visual sense in this age group are extremely difficult to make objectively; however, during the course of therapy, several observers were asked repeatedly to make an independent estimate of these functions, on a grossly clinical basis. It was the general impression that none of these patients showed worsening of their visual and auditory senses during the course of therapy and that in those treated for the longer periods of time, as D.M. and P.S., there had been slight but definite improvement in both these sensations.

As these children emerged from their clouded sensorial states and as they lost their muscular rigidity and spasticity, they all evidenced great weakness of all the major muscle groups. This weakness responded gradually to early physiotherapy and there was progressive return of normal muscular motion.

#### B. Temperature Course:

There were no dramatic temperature responses such as have been noted in occasional patients in the preliminary studies of meningeal or pulmonary tuberculosis reported by others. The earliest return of temperature to normal was observed in the case of L.L., who had defervescence after one week of therapy. The average length of time required for a return of temperature to normal was between three and six weeks. The fall in temperature was gradual over this period and this was followed by another period of four to six weeks in which there were occasional recrudescences of fever of mild degree usually lasting only a day or two without any accompanying clinical change. All patients are afebrile at the time of this report.

#### C. Cerebrospinal fluid course:

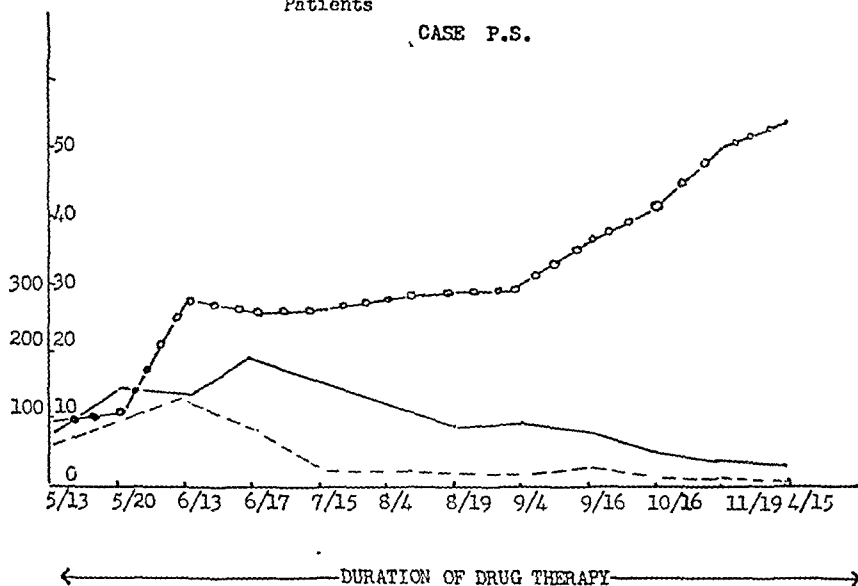
The response in the cerebrospinal fluid chemistry also was gradual in each case. The two patients, D.P. and J.S., without signs of meningeal irritation, but with characteristic spinal fluid changes, attained a normal spinal fluid within two months but the others required from four to six months to do so. The response of sugar, cells and protein in the two patients treated for the longest period of time, D.M. and P.S., is shown in Figure 1.

This roughly parallels the response observed in patients treated with streptomycin intramuscularly and intrathecally.

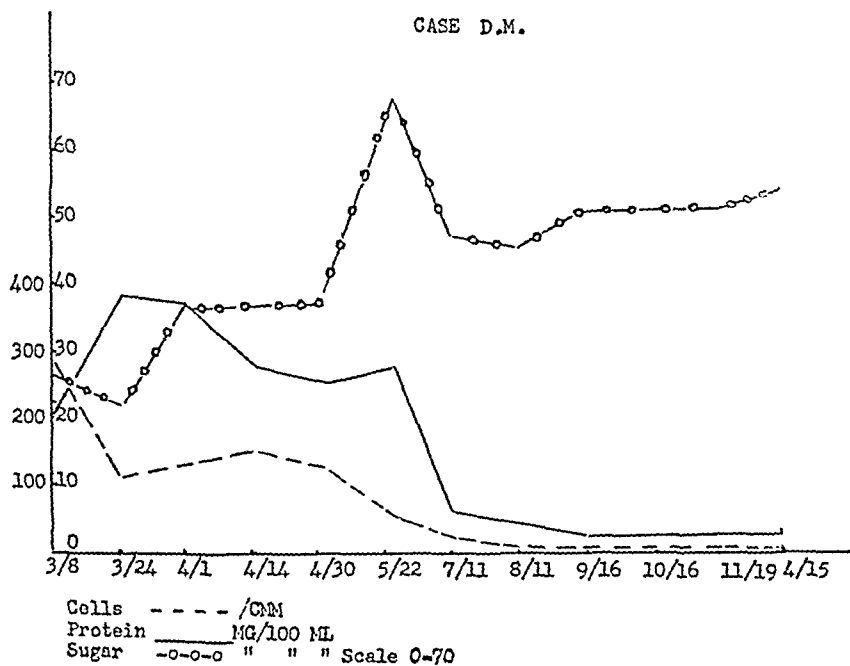
FIGURE I

Pattern of Response of Spinal fluid  
to Therapy with Streptomycin and  
Isonicotinic acid Hydrazide in Two  
Patients

CASE P.S.



CASE D.M.



The cerebrospinal fluid pressure returned to normal in all these patients but it did not show any fixed pattern of response. The fall to normal usually required between three and four months to occur. In none of these patients at any time during the course of therapy was there evidence of a block in the circulation of cerebrospinal fluid.

#### D. Bacteriological Response:

In three of the six children, J. S., L. L. and M. F., tubercle bacilli were isolated from the spinal fluid before the start of treatment. In only one case, L. L., was more than one positive culture for tubercle bacilli obtained, and this became negative within a period of three weeks after the initiation of therapy and has remained so. D. M., P. S. and D. P., who had had the longer periods of intramuscular streptomycin therapy before admission, did not show tubercle bacilli on repeated culture.

#### E. X-ray Film Changes:

Opportunity was afforded in the treatment of these patients to follow the course of their pulmonary tuberculosis under the influence of combined streptomycin and isoniazid therapy. The two who had miliary and associated tracheobronchial lymph node involvement had marked clearing of the pulmonary process within the first four months but there was slow retrogression of the lymph node foci. The three with combined pulmonary and lymph node involvement showed definite clearing of the parenchymal foci but little change in the lymph node components. Two of the latter, four to five months after initiation of therapy showed small areas suggestive of beginning calcification in the parenchymal lesions and one of them showed this change in the cervical lymph nodes also. The one patient with bilateral hilar lymph node enlargement without demonstrable pulmonary disease showed no change by serial roentgenograms.

#### F. Toxic Manifestations:

1) Hematopoietic System: There was no evidence in any of these patients of toxicity to the hematopoietic system during the prolonged usage of streptomycin and isoniazid. No significant eosinophilia was noted and there were no clinical evidences of increased bleeding tendency.

2) Urinalysis: Serial urine analyses did not reveal any evidences of marked renal toxicity to the therapeutic regimen. Each child had a faint trace of albumin on admission and intermittently during the course of treatment. There was no significant change in the cellular content of the urine. Occasional cylindroid and hyaline casts, and an occasional granular cast were seen, but no patient manifested any significant hematuria. The blood urea nitrogen was not altered in any case except once in J. S. without other signs or symptoms of renal toxicity.

3) Liver: Extensive liver function tests were not performed except for serial determinations of cephalin flocculation, thymol turbidity and the icteric index. Two infants, J. S. and D. P., developed, four months after the initiation of therapy, a 2+ cephalin flocculation test, and one, J. S.,

a thymol turbidity of 10.5 units. At no time did they have any evidence of hepatomegaly or jaundice, either clinical or biochemical and there were no correlative signs of liver disease. After the dose of INH was lowered to 5 mg. per kilo, thymol turbidity and cephalin flocculation gradually returned to normal.

4) Gastro-Intestinal Tract: Vomiting was a disturbing and severe complication in the early phases of treatment of all these patients. Most of them had relief of the vomiting when PAS was either stopped completely or the dosage reduced. Some did not respond to these measures and it may be that their vomiting was associated either with the use of streptomycin or was a result of the rise in the cerebrospinal fluid pressure, consequent to central nervous system inflammatory changes. Vomiting appeared to have no relation to the use of isoniazid orally or intramuscularly. In all cases after fluid replacement therapy and temporary cessation of oral feeding, the vomiting stopped and oral medications could be reinstituted.

5) Skin: Two infants developed transient erythematous maculopapular rashes, over the face, the upper trunk and the upper extremities. These disappeared within one or two days while both drugs were continued. No other cutaneous toxic manifestations were observed.

6) Central Nervous System: It was difficult to assess central nervous system toxicity in the presence of a disease with such overwhelming central nervous system manifestations as tuberculous meningitis. However, as the clinical state of the patient improved, frequent neurological examinations did not reveal any evidence of hyper-reflexia, muscular twitching or central nervous system stimulation described in earlier studies of isoniazid in adults.<sup>27</sup>

7) Cardiovascular System: There were no evidences at any time during the course of therapy of toxicity to the cardiovascular system from the use of these drugs. Electrocardiograms taken at the initiation of therapy and between four and six months after the use of isoniazid and streptomycin have revealed no evidences of myocardial toxicity.

#### *Levels of Streptomycin and Isoniazid*

Table II summarizes the data obtained on the simultaneous determinations of streptomycin and isoniazid in the plasma and spinal fluid at varying times after either an oral or intramuscular dose of isoniazid and intramuscular streptomycin. In the instances where two figures with an arrow between are recorded, these represent the range of values of a number of serial determinations. Two figures with comma represent two determinations. The plasma sample was taken no later than 10 minutes following the initiation of the lumbar tap. The streptomycin was given in the standard dose of 0.5 gm. intramuscularly once daily. The dose of isoniazid employed was the morning fraction of the total 10 mg. per kilogram daily dose of approximately 3.3 mg. per kilo. There was no significant difference in the levels obtained by oral or intramuscular administration of the drug. Plasma levels of isoniazid one and one-half hours after the dose varied from 1.5 to 6.7 mcg. per ml., from 0.5 to 5.8 mcg. per ml. at 5



TABLE II: Levels of Streptomycin and Isoniazid in Plasma and Spinal  
Fluid After I.M. or Oral Isoniazid and I.M. S.M.

	ONE AND A HALF HOURS AFTER DOSE			FIVE HOURS AFTER DOSE			TWELVE HOURS AFTER DOSE		
	I N H MCG/ML SP., FL. PL.	S M MCG/ML SP., FL. PL.	I N H MCG/ML SP., FL. PL.	I N H MCG/ML SP., FL. PL.	S M MCG/ML SP., FL. PL.	I N H MCG/ML SP., FL. PL.	I N H MCG/ML SP., FL. PL.	S M MCG/ML SP., FL. PL.	I N H MCG/ML SP., FL. PL.
J.S.	1.5 1.4	<1.0 20+	3.1, 2.3	5.8	0	-	2.0	1.0	-
M.F.	2.3 3.5	2.0 16.0	-	-	-	-	0.58	0.4	0.75 0.4
L.L.	3.8 6.1	20+ 20+	0.5, 1.6	0.5, 2.2	6.0	16.0	2.3	0.46	4.0 0
D.M.	4.7 6.5	0 16.0	0.67 → 4.0	0.24 → 5.7	0.75 → 6.0	20.0	1.2	0.65	0 0
P.S.	3.6 6.7	2.0 16.0	0.6 → 2.0	0.9 → 5.7	<1.0 → 8.0	20.0	1.2	0.65	1.0 0

hours and from 0.4 to 1 mcg. per ml. at 12 hours. The spinal fluid levels indicated ready passage of the isoniazid molecule into the spinal fluid, varying from 1.5 to 4.7 mcg. per ml. at one and one-half hours, from 0.5 to 4 mcg. per ml. at five hours and from 0 to 1 mcg. per ml. at 12 hours after the dose.

The minimal inhibiting level of isoniazid in mcg. per ml. has been found to vary from .025 to .25 mcg. per ml. depending upon the medium employed.<sup>6</sup> Considerably more than the adequate tuberculostatic concentration of isoniazid was obtained both in the spinal fluid and in the plasma in all these children one and one-half to five hours after an oral or intramuscular dose. Even 12 hours after such a dose, the majority of patients showed more than the minimal tuberculostatic concentration.

The low streptomycin levels reported in the spinal fluid in Table II were obtained in the patients D.M., J.S. and P.S., who had normal spinal fluids at the time of these determinations.

Corroborative evidence was obtained indicating that isoniazid entered the spinal fluid in significant tuberculostatic concentrations in two cases. This was suggested by the following experiment: Dilutions of the spinal fluid from D.M. and P.S. were made in the range of 1:6 to 1:24 in Dubos medium. The dilutions and a control were then seeded with a recently isolated sensitive, virulent strain of human type tubercle bacilli. A small amount of growth was obtained in the 1:24 dilution but none in any of the other tubes. Controls without spinal fluid grew readily. At the time these tests were performed both spinal fluids had been normal for more than three months and the streptomycin levels were less than 1 mcg. per ml. These patients did not receive PAS during this time.

### *Discussion*

Even a preliminary report on the clinical effectiveness of a therapeutic regimen ordinarily has little justification when limited to so small a number as six cases. However, the mortality rate in untreated tuberculous meningitis in infants is for all practical purposes 100 per cent within a relatively short period of time, rarely exceeding four to six weeks after the onset of the disease. The mortality of tuberculous meningitis in children when treated by the regimen of streptomycin intramuscularly and intrathecally approaches an overall rate of from 30 to 50 per cent in the earlier reported series.<sup>1,4,26,29</sup> More recent results have shown a further reduction of mortality. Lincoln<sup>31</sup> reports survival of two out of three infants when treated in that fashion. In the recent Public Health Service study,<sup>33</sup> there were 26 survivors out of 93 cases, 12 with gross residua. Most of the deaths, even in the series with optimal results, occurred within the first six or seven months, with the peak occurring within the first to the third month.

The infants in the study here reported present a group of cases in which the expected mortality even with the accepted regimen, would have been considerably higher than the overall rate. All were less than two years of age on admission, two were comatose and two were semicomatose, two had associated miliary tuberculosis, and four had impairment of visual

and auditory acuity. Debre<sup>26</sup> in a recent review of 262 cases of tuberculous meningitis in children treated with streptomycin by the standard technique showed the overall mortality of 50 per cent was greatly increased by the following factors, among others: (1) age under 18 months; (2) the presence of miliary tuberculosis; (3) disturbance in the state of consciousness on admission. It can be seen that all of the infants in this series had at least two of these factors for increased mortality present. For these reasons, we consider that this group, though small, provides a sample of sufficiently high mortality potential that the anti-tuberculous activity of any drug or combination of drugs could be manifested early in the course of treatment.

From the standpoint of clinical, bacteriological and cerebrospinal chemical findings, the regimen of streptomycin intramuscularly in association with isoniazid without intrathecal medication appears to have a decided effect on the course of tuberculous meningitis when compared against the two standards of the prognosis of the untreated disease and the prognosis using the optimal previous technique of streptomycin intramuscularly and intrathecally in association with a sulphone. These children have been treated for periods ranging from four to 13 months. All six have shown marked and progressive improvement in their clinical state and in their cerebrospinal fluid chemistry and cytology. All have gained weight and none has shown evidences of bacteriological relapse. All have achieved an afebrile state.

Without a properly controlled parallel series of patients treated on the regimen of intramuscular streptomycin in association with intrathecal streptomycin and a sulfone, no definite comparison can be made with the suggested regimen of streptomycin and isoniazid without intrathecal streptomycin. However, it appears that this therapeutic regimen has resulted in a response at least equivalent to that which one might expect from a regimen of streptomycin intramuscularly and intrathecally. The disadvantages of intrathecal therapy would seem to be avoided. In addition, it would seem that isoniazid with its high rate of diffusibility into the cerebrospinal fluid makes a positive contribution to the antibiotic and chemotherapeutic regimen. The period of observation is far too short to warrant any conclusion about eventual outcome or relapse or about residual impairment of mental faculties.

Even at this early date it can be stated that this is not the ideal or the final answer to the treatment of tuberculous meningitis. In this series, as in others, it is quite apparent that the eventual outcome depends to a very great extent upon the degree of damage to the central nervous system present at the time of admission. The improvement of results in any therapeutic regimen, this one included, therefore, depends to a great extent as Lincoln and others have emphasized, upon the early recognition of this complication.<sup>1,4,26</sup>

Isoniazid alone is probably not sufficient in the treatment of tuberculous meningitis. This seems to be the indication in the few cases which were so treated by Clark, et al.<sup>22</sup> Therefore, although this group of cases would seem to indicate that isoniazid makes a definite contribution to the use

of streptomycin, it is probable that here as in other types of tuberculosis, isoniazid is most effective as an adjuvant to streptomycin therapy.

No conclusion in such a small number of cases can be drawn as to the effect of this regimen on the focal neurological lesions so often present in the child with tuberculous meningitis. In the children who have attained normal spinal fluid, these focal signs are absent. In the two children observed for a shorter time, the focal signs are becoming less marked. Also, four of these children had diminution in visual and auditory acuity on admission. There has been a slight but gradual improvement in these senses during the course of treatment.

There is a difference between the degree of response of the meningeal and cerebral irritative phenomena such as opisthotonos, muscular rigidity, convulsions, etc., and the focal signs of neurological involvement. The more general signs disappear more rapidly with prompt subsidence of convulsive seizures; there was a less prompt but early and progressive loss of muscular rigidity. Only considerably later was there a loss of the signs of focal damage.

It is apparent that isoniazid can be given in the relatively high dosage of 10 mg. per kilogram in this age group without serious toxic manifestations. The minor degrees of albuminuria may or may not have been related to the use of this drug. It is not unlikely that these slight traces of albumin in the urine represent a less specific effect related to the presence of systemic infection, pyrexia, streptomycin, etc. There was no significant change in the blood urea nitrogen value among these patients. Further observations are, of course, necessary to decide whether this urinary finding becomes more marked with the use of this therapeutic combination over longer periods of time. Although fatty degeneration of the liver has been noted in dogs given higher dosage levels of isoniazid,<sup>15</sup> there was no evidence in any of these infants of a significant degree of hepato-toxicity. The two patients, J.S. and D.P., who showed some slight abnormality of the cephalin flocculation test and one, J.S., of the thymol turbidity, did not show any other evidence of hepatic damage. Further, because hepato-toxicity was feared, the dosage level was cut in half in these children and following this after three months, the thymol turbidity and cephalin flocculation became normal. It cannot be definitely stated whether the abnormalities were due to liver damage or were the result of changes of the serum protein as a result of the general systemic tuberculous process, since these are the patients who had associated miliary tuberculosis. Further observations are being carried out to detect early signs of hepatic damage in the other patients, but to date none has been observed.

Observations of the effect of streptomycin and isoniazid used together on the accompanying primary tuberculosis of the lungs in these infants cannot be any more than tentative since the number of cases is small, and the period of observation is relatively short. The marked improvement in the two miliary cases over a period of four months is in keeping with the observation of Clark, et al.<sup>22</sup> The parenchymal infiltrates in all showed rather prompt and marked clearing, but the lymph node involvement was

much slower to respond. It was felt by the roentgenologist that the degree of improvement noted has been observed in other patients at this hospital with similar pulmonary lesions though usually not with this rapidity. These results suggest that the employment of streptomycin together with isoniazid might be worthy of further investigation in the treatment of children with primary tuberculosis, particularly if they are clinically ill and if they have extensive parenchymal lesions.

Our data on the levels of isoniazid in the plasma and spinal fluid indicate easy passage of this molecule into the cerebrospinal fluid, as was observed by others.<sup>15,16</sup> Many times the minimal tuberculostatic concentration was obtained in both the plasma and the spinal fluid at one and one-half hours, and five hours, after a dose of isoniazid, either by mouth or intramuscularly. Even 12 hours after such a dose there were from two to 10 times the inhibiting concentration in the spinal fluid. Thus, it appears safe to administer isoniazid during the day in divided doses without the necessity of giving this drug during the night.

It appears also, in the two cases in which the point was investigated, that the biochemical assay of isoniazid is paralleled by the bacteriologic assay, as noted by Elmendorf, et al.<sup>16</sup> Patients D. M. and P. S. had significant tuberculostatic activity of their spinal fluids at a time when the chemistry and cytology had been normal for more than three months and when the streptomycin levels were less than 1 mcg. per ml.

Because of the ready diffusibility of the isoniazid molecule, both through inflamed and non-inflamed meninges, intrathecal isoniazid therapy may prove to be unnecessary in the majority of patients with tuberculous meningitis.

As reported by Lincoln<sup>19</sup> and others, we found that streptomycin entered the spinal fluid only when there was evidence of meningeal inflammation. As the cytology and chemistry of the spinal fluid showed improvement, the streptomycin level fell to zero or negligible values.

Furthermore, it has been shown that streptomycin intramuscularly without intrathecal use is of limited value in the treatment of tuberculous meningitis.<sup>29,30</sup> It is not to be expected that the results observed could have been obtained by the use of intramuscular streptomycin alone. It seems rather that the use of streptomycin and isoniazid together produces a clinical response in tuberculous meningitis which neither of these agents is capable of producing alone. This is in keeping with the recently reported observations of Mackaness on the survival rate of *M. tuberculosis* H37Rv in vitro and in mammalian macrophages in which activity was produced by the combined use of streptomycin and isoniazid.<sup>32</sup> Another advantage in the use of combined antituberculous agents is the delaying of bacterial resistance. Early indications are that this may be true in the case of streptomycin and isoniazid<sup>18,19</sup> (our own laboratory).

It is felt that prolonged treatment with streptomycin as well as isoniazid is necessary, even though streptomycin does not enter the spinal fluid in appreciable concentration when the evidences of meningeal inflammation have subsided. This is advisable not only to forestall the emergence of

bacterial resistance but also to obtain the effect of both drugs on bacilli which may still be present in the initial forms or in meningeal lesions from which relapse may occur. Dubos has re-emphasized the importance of this point<sup>28</sup> as have most of the clinical authorities. The observations of Mackaness and Smith<sup>32</sup> are pertinent in this regard also because they indicate that to obtain a combined effect of streptomycin and isoniazid, a relatively higher concentration of streptomycin must be maintained since this substance does not enter the cell to any great degree.

All these children are still under treatment at the time of this report. We intend to continue combined treatment for a period of one year. This would seem to be justifiable in view of the known proclivity of the disease to relapse and in view of the experience in the larger series of patients indicating better results with longer periods of therapy.

This series is too small to justify any statements on the effect of this therapeutic regimen in forestalling the appearance of cerebrospinal fluid block. However, none has occurred during the period of observation. This may be related to the absence of chemical irritation of streptomycin injected intrathecally as well as the greater diffusibility of isoniazid into tissue fluids and into cells so that living bacilli may be acted upon even when engulfed by macrophages, epithelioid cells or even fibrin.

#### ADDENDUM

Since we used PAS intermittently and irregularly during the acute phases of the disease, we were not able to evaluate its contribution to the therapeutic regimen in this series. Our clinical impression is that it is not essential to the therapeutic efficacy of the regimen. We do feel though that when it can be tolerated, it should be used for whatever tuberculo-static effect it may have. We would like to suggest its use during convalescence along with isoniazid.

We have used promizole only on two patients in late convalescence and do not feel justified in making any statements concerning its value. Further investigation of the value of PAS or promizole in addition to the basic streptomycin-isonicotinic acid hydrazide combination is justified.

D.M.: Progressive clinical improvement. Pulls himself up and walks around the crib, holding on to the sides. Recent spinal fluid values normal. Markedly diminished hearing and vision. Extreme lack of coordination. SM stopped July 14, 1953. Continues on IAH and PAS. To be discharged soon to continue drugs at home.

P.S.: Slow, progressive clinical improvement. Spinal fluid normal. SM stopped July 17, 1953. IAH continued and Promizole later added to regimen in place of PAS.

J.S.: Continued clinical improvement. Spinal fluid normal. SM stopped July 2, 1953. To continue IAH and PAS at home.

L.L.: Progressive clinical improvement. SM stopped November 1, 1953. Discharged November 1, 1953. To continue IAH and PAS at home. Spinal fluid normal

M.F.: Progressive clinical improvement. SM and IAH continued. Promizole recently added to regimen in place of PAS. Spinal fluid normal.

D.P.: Clinically well. Growing and developing normally. Spinal fluid normal. Normal intelligence. Continues SM, IAH and PAS. Would be ready for discharge to good home conditions which she does not have, and will be retained here.

## SUMMARY

1) Six infants, ranging in age from seven to 21 months, have been treated for tuberculous meningitis on a regimen of streptomycin and isoniazid 10 mg. per kilogram by mouth or by intramuscular injection. All were acutely ill on admission; four were comatose or semi-comatose and two had accompanying miliary tuberculosis.

2) These patients have been treated for periods ranging from four to 13 months. All have shown marked to moderate clinical improvement. The four treated for the longest periods of time have achieved a normal cerebrospinal fluid and have lost all evidence of meningeal irritation and of focal neurological lesions which were present on admission. None has shown any progression of disease and all have shown repeatedly negative spinal fluid cultures for tubercle bacilli and none has had a bacteriological relapse. None has developed cerebrospinal fluid block.

3) There was no evidence of any serious toxic manifestation as a result of the combined use of these drugs for prolonged periods of time. Transient slight albuminuria was frequently seen. Transient maculopapular rashes were seen in two cases and a disturbance of cephalin flocculation in two cases and thymol turbidity in one case. Despite continued therapy, these abnormalities have not persisted or progressed.

4) Significant levels of isoniazid were detected in the spinal fluid one and one-half hours, five hours and even 12 hours after either an oral or intramuscular dose of drug.

5) All these children had associated tuberculosis of the lungs. The patients with associated miliary tuberculosis of the lungs have shown marked improvement in the pulmonary and meningeal manifestations of their disease. Two other patients with parenchymal infiltration have shown marked to moderate improvement by serial roentgenographic examination.

6) It is felt, considering the mortality potential in this age group and with these clinical findings, that a definite favorable change in the course of tuberculous meningitis has been obtained. It is the clinical impression that these results are at least similar to what one would have expected with the regimen employing streptomycin systemically as well as intrathecally in association with or without a sulfone. The disadvantages of intrathecal therapy appear to have been avoided without a loss of bacteriostatic effect. Prolonged therapy on this regimen for a minimum of one year is suggested.

7) Further study of the use of streptomycin in combination with isoniazid in treatment of tuberculous meningitis would appear to be indicated.

The authors wish to express their gratitude to Miss Lillian Whitney, R.N., and the staff of the Children's Division for energetic and enthusiastic nursing care and to Dr. Edmund H. Kerper, for assistance in the interpreting of roentgenograms.

## RESUMEN

1) Se trataron seis niños de 7 a 21 meses de edad con meningitis tuberculosa por medio de estreptomicina:  $\frac{1}{2}$  gmo. diario e isoniácida: 10 mg. por kilo, por vía oral o intramuscular. Todos se encontraban severamente

enfermos a su ingreso; cuatro comatosos, o semicomatosos y dos, tenían además, tuberculosis miliar.

2) Estos enfermos se trataron por períodos de 4 a 13 meses. Todos tuvieron mejoría clínica moderada o marcada. Los cuatro tratados por período más largo, han llegado a tener líquido cerebroespinal normal, y en ellos, ha desaparecido toda evidencia de irritación meníngea así como de las lesiones neurológicas focales que presentaron a su ingreso. Ninguno ha mostrado un empeoramiento de la enfermedad y ninguno ha tenido recaída bacteriológica. Ninguno ha tenido bloqueo del líquido cerebroespinal.

3) No hay evidencia de manifestación tóxica alguna como resultado de la combinación de estas drogas por períodos largos de tiempo. Se ha visto albuminaria frecuente transitoria. Manchas cutáneas maculopapulares se vieron en dos casos y alteraciones de la cefalín floculación en dos casos y turbidez al timol en uno. A pesar de la continuada terapéutica, estas alteraciones, no persistieron ni progresaron.

4) Se encontraron tenores significantes de isoniácida, en el líquido espinal una hora y una y media horas, así como cinco y aún 12 horas después de la administración oral o intramuscular de la droga.

5) Los enfermos con miliar asociada en los pulmones, mostraron marcada mejoría en las manifestaciones meníngeas y pulmonares de la enfermedad. Otros dos enfermos con infiltración parenquimatosa, mostraron mejoría marcada según la serie radiológica.

6) Se cree, considerando el elevado potencial de mortalidad de este padecimiento en esta edad, que se ha obtenido un cambio definido favorable en la evolución de la meningitis tuberculosa. La impresión clínica, es que estos resultados cuando menos, son similares a los que se esperarían empleando estreptomycina parenteral al mismo tiempo que intratecal, con asociación de una sulfona. Las desventajas de la terapéutica intratecal, parecen haber sido evitadas sin una pérdida de efecto bacteriostático. Se sugiere el tratamiento prolongado con este régimen por un mínimo de un año.

7) Parecen indicados ulteriores estudios sobre el uso de la estreptomycina combinada con la isoniácida en la meningitis tuberculosa.

### RESUME

1) Six enfants âgés de 7 à 21 mois atteints de tuberculose méningée, ont été traités par 50 cgr. de streptomycine et 10 mmgr. d'isoniazide par kilogramme, soit par voie buccale, soit par injection intramusculaire. Tous étaient en période aigue lors de leur admission, quatre étaient comateux ou semi-comateux et deux avaient une tuberculose miliaire associée.

2) Ces malades ont été traités pendant un laps de temps allant de quatre à treize mois. Tous ont montré une amélioration clinique soit très nette, soit modérée. Les quatre enfants qui ont été traités pendant la temps le plus long ont fini par avoir un liquide céphalo-rachidien normal, et ne présentent plus aucun signe d'irritation méningée, ou de lésions neurologiques localisées, telles qu'ils en avaient au moment de leur admission. Chez aucun d'entre eux, l'affection n'a continué à évoluer, tous ont actuel-



lement un liquide céphalo-rachidien dépourvu de bacilles, même à la culture, et il n'y a eu aucune rechute bactériologique. Aucun de ces malades n'a eu de blocage du liquide céphalo-rachidien.

3) Les auteurs n'ont constaté aucune manifestation toxique sérieuse, à la suite de l'utilisation de ces drogues associées pendant une période de temps prolongé. Une légère albuminurie transitoire a été notée souvent. Dans deux cas, apparurent des rashes de type maculopapuleux et transitoire. Deux malades eurent un trouble de la floculation à la céphaline, et l'un une opacification au thymol. Ces anomalies n'ont ni persisté, ni progressé malgré la continuation du traitement.

4) Des taux importants d'isoniazide furent constatés dans le liquide céphalo-rachidien, une heure, une heure et demie, cinq heures et même douze heures après administration de ce produit par voie bucale ou intramusculaire.

5) Tous ces enfants étaient atteints de tuberculose pulmonaire associée. Les malades qui avaient une atteinte miliaire des poumons associée montrèrent une amélioration notable à la fois des manifestations pulmonaires et méningées. Chez deux autres malades atteints d'infiltration parenchymateuse, des radiographies en séries ont montré une amélioration marquée ou modérée.

6) Les auteurs considèrent, étant donné la mortalité habituelle à l'âge des malades qu'ils ont étudiés et avec les symptômes qu'il ont eus, qu'ils ont obtenus une modification tout à fait favorable de l'évolution de la méningite tuberculeuse. Ces résultats donnent l'impression qu'ils sont au moins semblables à ce que l'on pourrait attendre d'un traitement systématique à la streptomycine intra-rachidienne associée ou non aux sulfones. Les inconvénients du traitement intra-rachidien semblent avoir été évités sans que l'on ait perdu une part de l'action bactériostatique. Les auteurs proposent que le traitement qu'ils emploient soit prolongé au minimum pendant une année.

7) Il semble indiqué de continuer à étudier l'utilisation combinée streptomycine-isoniazide dans le traitement de la tuberculose méningée.

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# Tryptar in Intrathoracic Disease\*

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Tryptar is a brand of highly purified crystalline trypsin prepared from mammalian pancreas glands. The enzyme is stable indefinitely at room temperature but when placed in solution approximately 50 per cent of the proteolytic activity is dissipated within four hours. For this reason, tryptar solutions should be prepared freshly each time before use.

Tryptar is effective over a pH range of 5 to 8, exhibiting its greatest activity at about pH of 7. It has a broad spectrum of hydrolytic activity on proteins degrading them to small polypeptides and some amino acids. There is a considerable differential in the destruction of various groups of proteins by tryptar since denatured protein and flat chain molecules, such as fibrin and fibrinogen, are hydrolyzed much more rapidly than other proteins.

Tryptar is not active upon and does not harm living tissues since it has shown that trypsin does not penetrate the viable cell membrane. In addition, each cell contains a specific trypsin inhibitor which protects the cell from proteolytic action of the enzyme. Serum also contains specific and non-specific trypsin inhibitors which counter the effects of tryptar.

Signs of sensitization or clinical antigenicity to tryptar have not been observed. The enzyme may be safely used over prolonged periods or recurrently after long intervals.

Tryptar is a useful agent to the surgeon to remove intrapleural deposits of fibrin.<sup>1</sup> The following reports of cases show the indications, methods, limitations and results obtained from its use for these purposes.

## *Report of Cases*

*Case 1:* A 25 year old Negro man, admitted to the hospital on April 6, 1952, had incurred a stab wound of the left side of the chest on April 5, 1952. He had been admitted first to another hospital then transferred to this hospital. The roentgenogram of the chest on admission showed fluid in the left pleural cavity (Figure 1). Intercostal closed catheter drainage, to which suction of about —20 cm. of water was connected, was provided on April 6. Tryptar,† 250,000 Armour units in 20 cc. of Sorenson's Phosphate Buffer Solution was injected through the catheter twice a day from April 7 through April 14. The catheter was clamped for four hours to permit digestion and then suction was reapplied. He was given penicillin and cholormycetin. He also received benedryl in doses of 0.1 gram for the first dose and then 0.05 gram four times a day. The roentgenogram of April 10 (Figure 2) showed little change. The quantity of aspirated blood decreased and the fluid

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†The Tryptar was supplied by The Armour Laboratories.

became serous so that it was possible to remove the catheter on April 14. A considerable diminution in the quantity of fluid in the pleural cavity was noted on the roentgenogram of April 17 (Figure 3). He was discharged from the hospital on April 21. On May 21, he stated that he was asymptomatic and was working at his usual occupation. The roentgenogram of May 21 showed slight thickening of the pleura and obliteration of the costophrenic angle on the left side (Figure 4).

*Case 2:* A 26 year old Negro man, admitted to the hospital on May 2, 1952 had incurred a stab wound of the right side of the chest on the same day. He had been admitted previously to another hospital where about 500 cc. of blood had been aspirated from the right pleural cavity. He had been transferred to this hospital

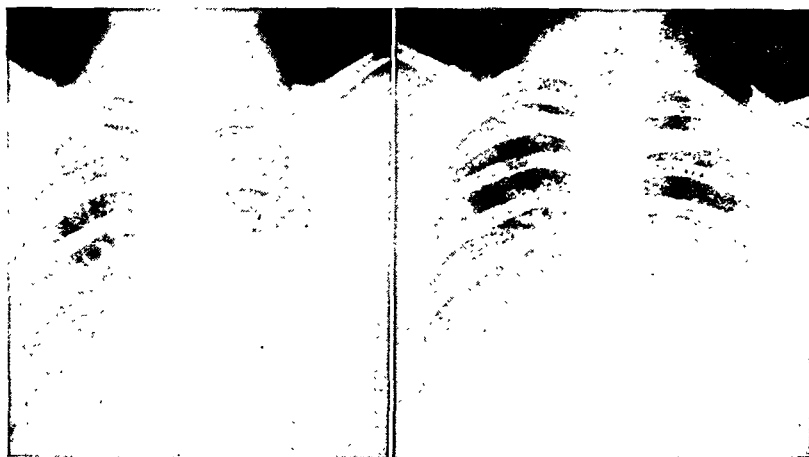


FIGURE 1

FIGURE 2

*Figure 1:* Left hemothorax on April 6, 1952.—*Figure 2:* Left hemothorax after intercostal closed catheter drainage and treatment with Tryptar on April 10, 1952.



FIGURE 3

FIGURE 4

*Figure 3:* Left hemothorax on April 17. Catheter has been removed.

*Figure 4:* Roentgenogram of chest on May 21.

for further care. The roentgenogram of the chest on May 2 showed a moderate amount of fluid in the right pleural space. Upon aspiration, this was found to be sanguineous. Intercostal closed catheter drainage with suction of about -20 cm. of water was provided on May 2, with about 300 cc. of sanguineous fluid being removed at the time of operation. The patient was given penicillin and benedryl. Tryptar, 200,000 Armour units in 25 cc. of Sorenson's phosphate buffer solution, was injected through the catheter twice a day from May 3 through May 7. The catheter was clamped for three hours to permit digestion after which suction was re-established. The quantity of sanguineous fluid had decreased and the fluid had become serous, so the catheter was removed on May 12. The roentgenogram of

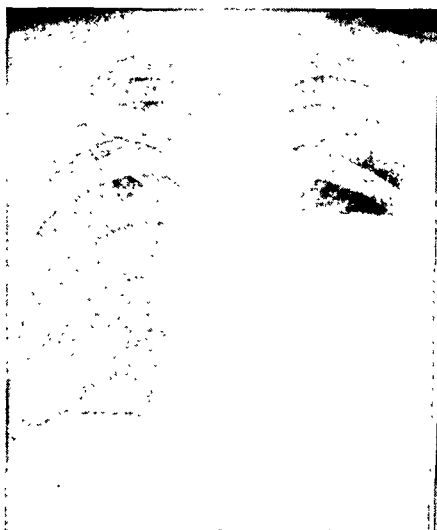


FIGURE 5



FIGURE 6

*Figure 5: Left empyema on February 28, 1952.—Figure 6: Left loculated collection of fluid with overlying air on March 21, 1952.*



FIGURE 7



FIGURE 8

*Figure 7: Roentgenogram showing diminution of fluid in left pleural cavity on April 5, 1952.—Figure 8: Roentgenogram of chest on April 24, 1952.*

May 12 showed a decreased amount of fluid while that of May 20 showed some thickening of the pleura in the lower part of the chest with blunting of the costophrenic angle. He was discharged from the hospital on May 20. On June 20, he stated that he was asymptomatic. The roentgenogram of June 20 showed some resolution of the thickening of the pleura.

*Case 3:* A 46 year old white man was admitted to the surgical service on February 8, 1952 for the treatment of pain in the back and over the left ilium for about 17 years which was due to rheumatoid arthritis. He denied having symptoms referable to the lungs although the physical examination indicated that pneumonitis and pleural effusion were present on the left side. The roentgenogram of the chest made on February 9 showed left pneumonitis and pleural effusion. About 1,200 cc. of fluid were aspirated from the pleural cavity on February 16. Aerobic and anaerobic cultures of the fluid were sterile. Acid-fast bacilli were not found by smear or culture. Repeated examinations of the sputum and gastric washings were negative for acid-fast bacilli. He was given penicillin, aureomycin and terramycin at various times during the stay in the hospital. He was transferred to the medical service for further care. The effusion (Figure 5), however, subsequently became purulent and about 50 cc. of foul-smelling green pus were aspirated from the pleural cavity on March 3. A *Streptococcus anaerobius* and a microaerophilic *Streptococcus viridans* were cultured from the pus. He was transferred back to the surgical service and an intercostal closed catheter drainage with suction of about -20 cm. of water was provided on March 3. He was given benedryl. Tryptar, 200,000 Armour units in 20 cc. of Sorenson's phosphate buffer solution, was injected through the catheter twice a day from March 3 through March 7. The catheter was clamped for four hours after the injection of tryptar to permit digestion after which the suction was re-established. About 1,500 cc. of pus were aspirated during the first 24 hours. Repeated roentgenograms showed progressive resolution and when the fluid became serous on March 10, the catheter was removed. A loculated collection of fluid with overlying air was noted on March 21 (Figure 6) and this was thought to be the result of bronchopleural fistula. Intercostal closed catheter drainage with suction was re-established on March 21. Tryptar was given in a similar manner from March 22 through April 1. The suction



FIGURE 9



FIGURE 10

*Figure 9:* Right pleural effusion on March 15, 1952.—*Figure 10:* Right empyema after intercostal closed catheter drainage and treatment with Tryptar on March 26, 1952.

was discontinued and the catheter cut at the chest wall on April 5. The roentgenogram on April 5 showed considerable diminution in the quantity of the fluid (Figure 7). The catheter was removed on April 7. An excellent response was obtained. On April 10, roentgenograms showed some thickening of the pleura. The wound healed and the patient was transferred to the medical service for further care of the rheumatoid arthritis. The roentgenogram of April 24 showed only a blunting of the costophrenic sinus (Figure 8). He was discharged from the hospital on May 8.

*Case 4:* A 31 year old white man, admitted to the medical service on March 15, 1952 with a history of having a respiratory infection for three weeks, was found to have pneumonitis with pleural effusion on the right side (Figure 9). Aureomycin, penicillin and terramycin were given at various periods during the stay in the hospital. Pus, from which pneumococci were cultured, was aspirated from the pleural cavity on March 18. He was transferred to the surgical service on March 18 and a closed intercostal catheter drainage, with suction of about -20 cm. of water, was provided on the same day. He was given benedryl. Tryptar, 200,000 Armour units in 30 cc. of Sorenson's phosphate buffer solution was injected through the catheter three times a day from March 18 through April 11. The dose was changed to 250,000 units in 20 cc. once a day from April 12 through April 25. The catheter was clamped for four hours after each injection to permit digestion after which the suction was re-established. About 1,800 cc. of pus were aspirated from the pleural cavity in the first 24 hours. A bronchopleural fistula was noted on March 25. Considerable improvement was seen on the roentgenogram of March 26 (Figure 10) with slight additional progress being noted on April 5 (Figure 11). Repeated roentgenograms showed progressive improvement so that it was possible to remove the catheter on April 26. A peripheral zone of increased density over the right lung with obliteration of the right costophrenic sinus was seen on the roentgenogram of May 6 (Figure 12). He was discharged from the hospital on May 9.

*Case 5:* A 34 year old Negro man was admitted to the medical service on May 21, 1952 with pain in the right side of the thorax. A diagnosis of bronchopneumonia and pleurisy with effusion on the right side was made. He was treated with aureo-



FIGURE 11



FIGURE 12

*Figure 11:* Right empyema on April 5, 1952.  
*Figure 12:* Roentgenogram of chest on May 6, 1952.

mycin. About 250 cc. of dark amber fluid were aspirated from the right pleural cavity on May 27. The fluid was sterile in aerobic and anerobic culture. The temperature, however, continued to be moderately elevated. He was subsequently seen in consultation by the surgical service. Aspiration of a loculated area in the right pleural cavity produced about 3 cc. of foul-smelling pus, cultures of which were sterile, aerobically and anaerobically. He was transferred to the surgical service. Intercostal closed catheter drainage with suction of about -20 cm. of water was provided on June 23. At the time of operation about 40 cc. of malodorous pus was aspirated. He received penicillin at this time. Tryptar, 200,000 Armour units in 15 cc. of Sorenson's phosphate buffer solution, was injected through the catheter twice a day from June 24 through June 30. The catheter was clamped for about three hours after injection to permit digestion and then suction was re-established. Benedryl was given during this period. During the treatment with Tryptar, the pus became much thinner. The catheter was removed on July 6. He was discharged from the hospital on July 14. At a follow-up examination on August 14, he was asymptomatic. The roentgenogram of August 14 showed only an area of thickening of the pleura in the right cardiophrenic angle.

Case 6: A 35 year old white man, admitted to the medical service on December 31, 1951 had had a sudden onset of pain in the left side of the chest about one week previously. It was associated with a non-productive cough and fever of an undetermined height. The patient had incurred a gunshot wound of the left side of the chest in 1943. The injury was complicated by empyema which necessitated performance of several operations. The temperature was elevated to 101 degrees F. The roentgenogram of January 3, 1952 (Figure 13) showed left pleural effusion. On January 4, pus was noted draining from the mid-portion of the scar on the left side of the chest wall. *Staphylococcus aureus* was cultured. He was seen in consultation by the surgical service on January 4 when the diagnosis of an empyema necessitans was apparent. He was transferred to the surgical service and an unroofing of the empyema cavity was done on January 4. About 200 cc. of thick pus were evacuated. Two number 18 French catheters were placed into the base of the wound which was packed open with nylon gauze. Suction of about -20 cm. of water was applied to the catheters in turn. He was given penicillin and

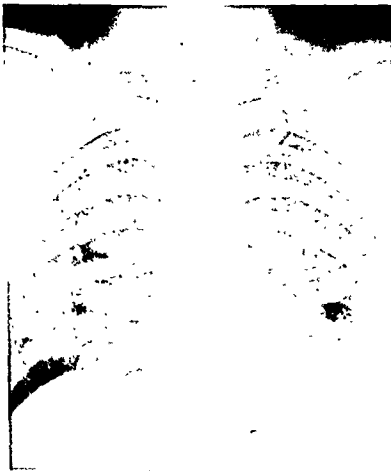


FIGURE 13

*Figure 13: Left pleural effusion on January 3, 1952.*



FIGURE 14

*Figure 14: Wound on January 10, 1952.*



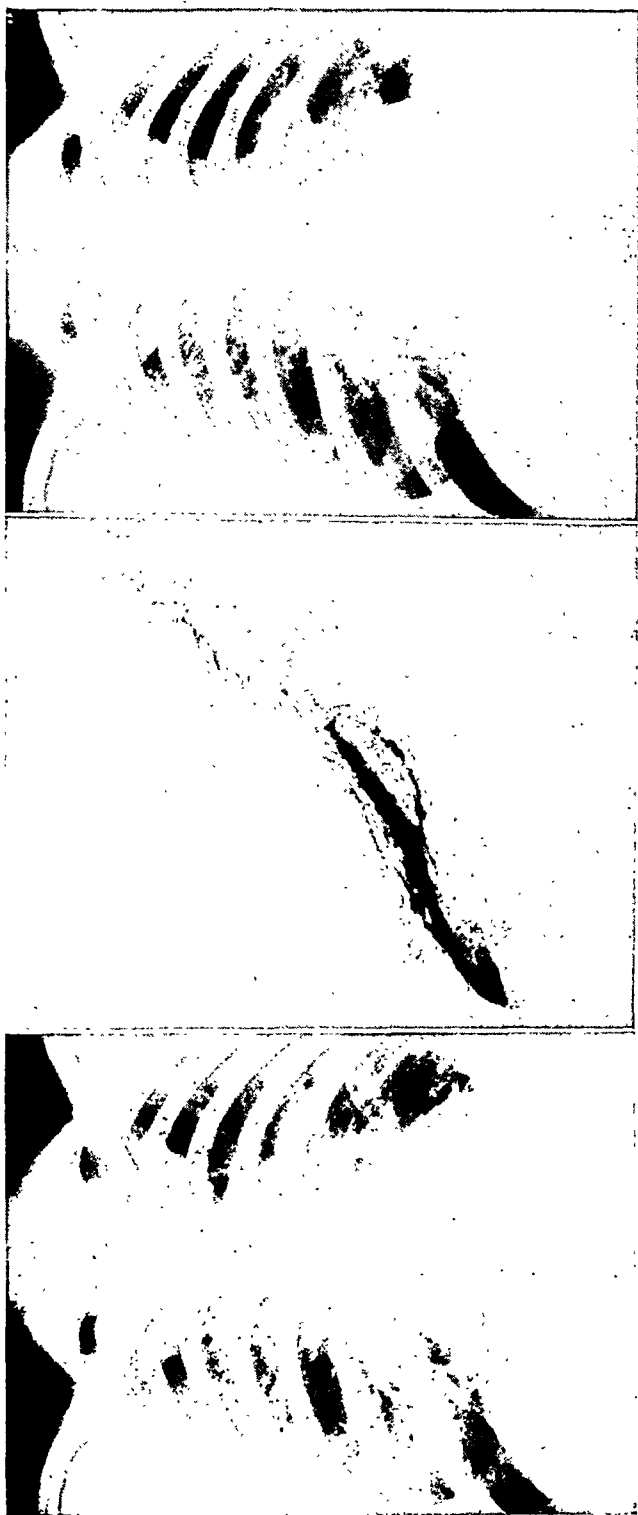


FIGURE 15

FIGURE 16

FIGURE 17

*Figure 15: Roentgenogram of chest on January 14, 1952.*

*Figure 16: Wound on January 15, 1952.*

*Figure 17: Roentgenogram of chest on January 28, 1952.*

sulfadiazine at various times during the stay in the hospital. Tryptar, 100,000 Armour units in 10 cc. of Sorenson's phosphate buffer solution was injected through one of the catheters daily from January 5 through January 8. The catheters were clamped for four hours to permit digestion and then the suction was re-established. The pack and catheters were removed from the wound on January 8. Tryptar powder was blown into the wound (Figure 14) to form a fine film by a DeVilbiss blower once daily from January 9 through January 15. The roentgenogram of January 14 showed considerable improvement (Figure 15). The wound (Figure 16) became clean. Partial thoracoplasty and closure of the wound was done on January 16. A number 20 French catheter was placed into the base of the wound. Tryptar, 33,000 Armour units in 5 cc. of Sorenson's phosphate buffer solution was injected through the catheters into the wound every six hours from



FIGURE 18

*Figure 18: Wound on February 19, 1952.*



FIGURE 19

*Figure 19: Roentgenogram of chest on May 2, 1952.*

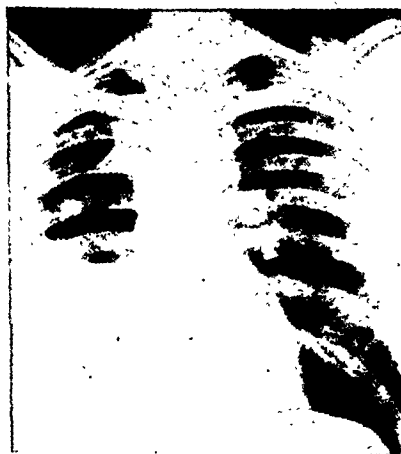


FIGURE 20

*Figure 20: Collapse of right lung and pleural effusion on December 19, 1951.*

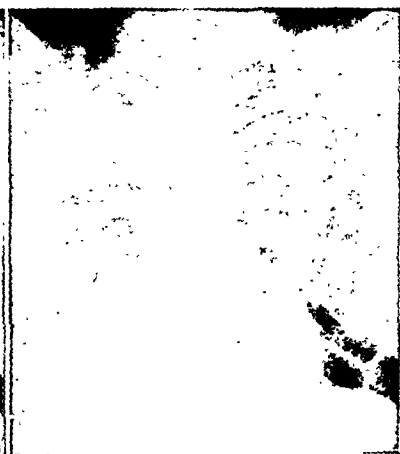


FIGURE 21

*Figure 21: Roentgenogram of chest on January 23, 1952.*

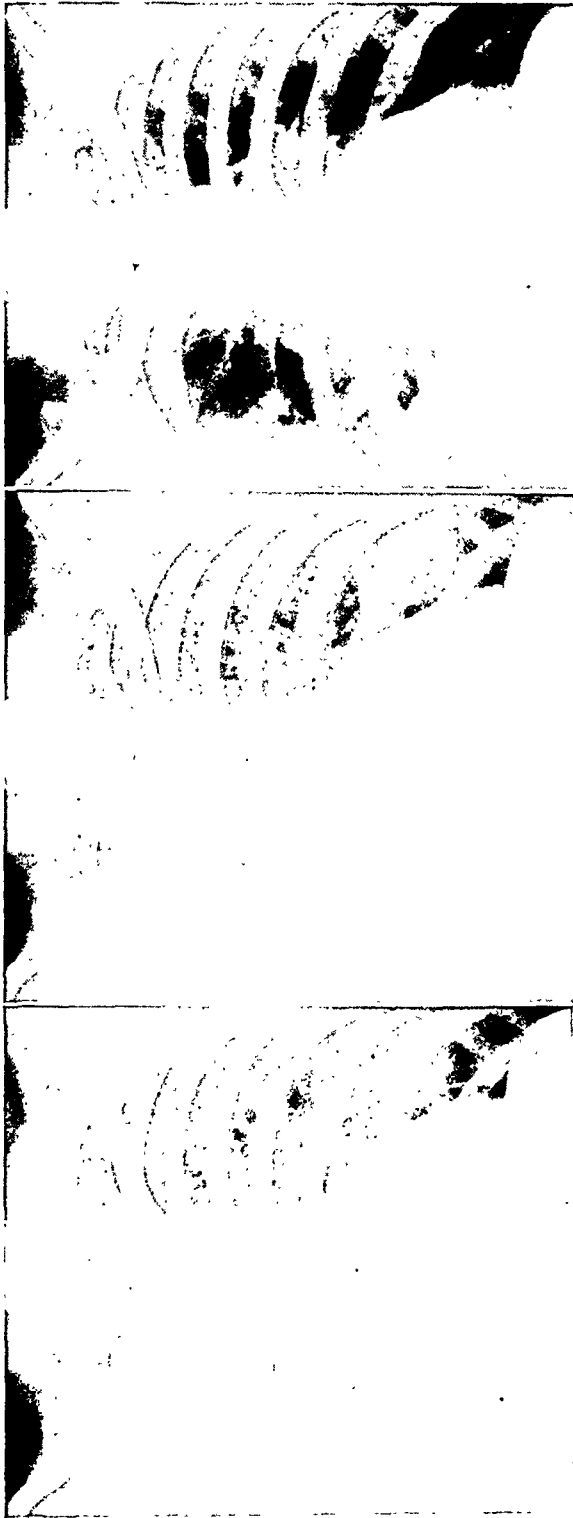


FIGURE 22

*Figure 22: Roentgenogram of chest on January 29, 1952.*

*Figure 23: Roentgenogram of chest on February 11, 1952.*

*Figure 24: Roentgenogram of Chest on June 12, 1952.*

FIGURE 23

FIGURE 24

January 17 through January 24. The catheter was clamped for four hours to permit digestion and then the suction was re-established. He was given benedryl. During this period 20 cc. to 50 cc. of sanguiniferous fluid were aspirated from the wound daily. The catheter was removed from the wound on January 24 when the main portion was healed. The roentgenogram of January 28 (Figure 17) showed improvement. The tract of the catheter was healed on February 14. The wound (Figure 18) looked good on February 19. He was discharged from the hospital on February 19. On May 2, he stated that he was well and was working full-time as a truck driver. The roentgenogram of May 2 (Figure 19) showed a slight collapse of the lateral wall on the left side and clear lungs.

**Case 7:** A 25 year old white man, admitted to the hospital on May 4, 1952, had had bronchiectasis for seven years. Bronchography showed dilatation and saccululation of the lingula of the upper lobe and all of the basilar segments of the lower lobe of the left lung and minimal changes in the anterior segment of the right lung. On May 28, the lingula and the basilar segments were resected. Intercostal closed catheter drainage with suction of about -20 cm. of water was provided. However, hemothorax formed postoperatively. Benedryl was administered. Tryptar, 200,000 Armour units in 25 cc. of Sorenson's phosphate buffer solution was injected through the catheter into the pleural space twice a day for 11 days. The catheter was clamped for three hours after each injection after which suction was re-established. Large amounts of sanguineous fluid were aspirated from the pleural cavity. The roentgenograms showed progressive improvement. The catheter was removed on June 18. The temperature however, became elevated and foul-smelling pus was aspirated from the pleural cavity on June 24. *Escherichia coli* and an unidentified micrococcus were cultured from the pus. Intercostal closed catheter drainage with suction was re-established on June 25. Tryptar was injected into the pleural cavity in a similar manner from June 26 through June 30 when the injections were discontinued due to a lack of the agent. The injections of tryptar were resumed from July 10 through July 14. The infection, however, was not controlled. The pocket was unroofed by resection of the overlying rib on July 15. About 30 cc. of pus were evacuated from the loculation. A small bronchopleural fistula was found at the medial part of the wound. The wound was packed open with nylon into which plain gauze was placed. Tryptar was blown into the wound to form a fine film by a DeVilbiss blower from July 17 through August 4. The cavity gradually became clean. The wound was closed on August 5. The pocket then measured 6 by 3 by 3 cm. and the bronchopleural fistula was still present. The overlying ribs were resected and the intercostal muscles sutured in such a manner as to occlude the bronchopleural fistula. Two number 20 French catheters were inserted into the depths of the wound for air-vent suction and brought out through its anterior end. Flaps of muscle were developed and the pocket filled. Suction of about -20 cm. of water was applied to the catheters which were removed on August 11. The wound healed well. He was discharged from the hospital on September 9 to return for observation for the bronchiectasis in the upper lobe of the right lung. On October 9, he stated that he did not have dyspnea. Very little expectoration was noted although occasionally the sputum was tinged with blood. He had gained 8 pounds. The roentgenogram of October 9 showed some clouding of the lower third of the left lung field. On November 21, he stated that he felt well. He had a little expectoration which was not tinged with blood. The bronchogram of November 21 showed minimal bronchiectasis of the anterior segment of the upper lobe of the right lung.

**Case 8:** A 56 year old white man, admitted to the hospital on September 14, 1951, had right pneumonectomy for bronchogenic carcinoma on October 9. A bronchopleural fistula was noted on December 10. An intercostal closed catheter drainage, to which suction of about 20 cm. of water was applied, was provided on December

10. A large amount of pus was obtained. Although his general condition improved, the fistula persisted. Suction was discontinued and a short segment of catheter to act as a drain was inserted into the pleural cavity. He was discharged from the hospital to the care of his local physician on February 9, 1952. On his return to the hospital on March 18, the fistula was still present. A catheter was inserted and tryptar, 200,000 Armour units in 5 cc. of Sorenson's phosphate buffer solution was injected once a day from March 23 through April 9. He was postured for two hours to retain the solution. The pus decreased in amount by 50 per cent, became less viscid and lost a part of the foul odor. Evidence of a spread of the infection into the left lung was not seen. On April 11, first stage anterior thoracoplasty was done. He was given penicillin. The drainage from the catheter decreased in amount. The operative wound healed. On May 1, second stage posterior thoracoplasty was done. The fistula closed on May 2. The operative wound healed. *Proteus vulgaris* was cultured from the pus at the site of the drainage. The tract for the catheter healed on May 17. He was discharged from the hospital on May 23, but was admitted to another hospital on June 14 critically ill with dyspnea, cyanosis and jaundice. He died shortly after admission with the autopsy showing pus in the right pleural space, acute and chronic myocarditis and chronic passive congestion of the liver, spleen and kidneys with toxic degeneration.

*Case 9:* A 63 year old white man was admitted to the medical service on January 28, 1952 for atelectasis of the middle part of the right lung. A diagnosis of tuberculosis of the peritoneum had been made elsewhere previously with enlarged liver and spleen being found at operation. In March 1952, he developed pleural effusion on the right side. Repeated examinations of sputum, gastric washings and fluid from the right pleural cavity were negative for acid-fast bacilli. He was transferred to the surgical service for observation, investigation and further treatment of his disease. Intercostal closed catheter drainage with suction was established on May 23. Tryptar, 200,000 Armour units in 30 cc. of Sorenson's phosphate buffer solution was injected into the right pleural cavity daily from May 23 to June 3. Large amounts of sanguineous fluid were aspirated from the pleural cavity but only moderate clearing occurred. The catheter was removed on June 3. Sanguineous fluid was thereafter obtained by aspiration at irregular intervals. The leukocyte count which was 14,100 per cmm. on June 5 rose to 43,200 per cm. on July 1. Purulent fluid was subsequently aspirated from the right pleural cavity. Right thoracotomy to obtain pleura or lung for biopsy and to provide drainage was done on July 22. A moderate amount of necrotic debris and clotted blood was present. The lower lobe was decorticated. The underlying lung was free of disease. Intercostal closed catheter drainage was provided. Biopsy showed tuberculous pleurisy and occasional acid-fast bacilli were demonstrated. Streptomycin and hydrazid were started but he did poorly. The leukocyte count rose to 260,200 per cmm. and then to 302,500 on August 30. Although it was strongly suspected during the long period of illness that he had chronic myeloid leukemia, it was the feeling of the hematologist that the elevated leukocyte count was due to a leukemoid reaction. He died on August 30. Tuberculous empyema with secondary infection of the right side, extensive tuberculosis of the lymph nodes and chronic myeloid leukemia were found at autopsy.

*Case 10:* A 26 year old Negro man had resection of the upper lobe and the superior segment of the lower lobe of the right lung and thoracoplasty done for tuberculosis on May 29, 1952. One catheter was brought out in the first intercostal space in the anterior axillary line and a second in the eighth intercostal space in the posterior axillary line. A water seal was provided for the anterior catheter while suction of about -20 cm. of water was applied to the posterior catheter. Due to excessive drainage of sanguineous fluid from the chest, the suction was discontinued in a short time after operation. About 1,300 cc. of sanguineous fluid

were aspirated from the chest during the first 24 hours after operation. Since the posterior catheter was not functioning, it was removed on May 31. Aspiration of the pleural space produced only a few cc. of blood. The roentgenogram of June 2 showed a diffuse density over the right side and it was apparent that clotted hemothorax was present. The anterior catheter was removed and closed intercostal catheter drainage through the fifth space to which suction of about -20 cm. was attached, was provided on June 2. He was given benedryl. Tryptar, 200,000 Armour units in 25 cc. of Sorenson's phosphate buffer solution, were injected through the catheter four times a day from June 3 through June 7. The catheter was clamped for four hours after injection to permit digestion after which suction was re-established. About 375 cc. of sanguineous fluid were aspirated during the first 24 hours after treatment with tryptar was started and about 800 cc. during the second. Additional fluid was not obtained. The catheter was removed on June 10. Bronchoscopy with aspiration of a moderate amount of secretion was done on June 5 and repeated on June 9 when only a small amount of mucoid secretion was obtained. Tryptar, 50,000 Armour units in 10 cc. of Sorenson's phosphate buffer solution, was put into the right main bronchus through a catheter passed through the bronchoscope. Repeated roentgenograms showed progressive resolution of the effusion and on June 16, the lower lobe was considerably expanded. He was transferred to the medical service for further care on July 7. On July 30, the roentgenogram showed further expansion of the lower lobe with considerable resolution of the effusion. On November 10, the roentgenogram showed good aeration of the remaining portions of the right lung and only minimal thickening of the pleura.

*Case 11:* A 34 year old Negro man, admitted to the surgical service on December 17, 1951 was found to have tuberculosis of the right lung in August 1944. He was on bed rest until June 1945 when pneumothorax was established and continued until August 1949. At the time of re-examination in November 1950, hydropneumothorax was present. Sanguineous fluid was aspirated from the pleural cavity in January 1951 and during the next three months. The sputum had been negative for acid-fast bacilli since 1945. He was referred to the hospital for decortication of the right lung. Repeated examinations of the sputum and gastric washings were negative for acid-fast bacilli. The roentgenograms of the chest showed 50 per cent collapse of the right lung with a fluid level at the seventh rib posteriorly (Figure 20). Closed intercostal catheter drainage was provided on January 2, 1952. Five injections of tryptar, 200,000 Armour units, in 20 cc. of Sorenson's phosphate buffer solution were given at irregular intervals between January 2 and January 17. Benedryl was administered. He also received penicillin and chloromycetin. The fluid in the pleural cavity was serous at first. During the treatment with tryptar, large amounts of fibrinous material were noted in the aspirated fluid but blood was never seen. The temperature became elevated to as high as 104 degrees F. during this period. The lung, however, did not expand (Figures 21 and 22) and decortication was done on February 7. A moderate amount of fibrinous material was still present in the pleural cavity although the pleural space was clean. The peel was about 0.6 cm. thick in some places. Intercostal closed catheter drainage with suction of about -20 cm. of water was provided. The roentgenogram showed good progress (Figure 23) and the catheter was removed on February 18. He was discharged on March 11. On June 12, he stated that his activity was normal although he had not yet returned to work. The roentgenogram of June 12 (Figure 24) showed slight thickening of the pleura over the lateral surface of the right lung with obliteration of the costophrenic sinus.

#### *Comment*

The results obtained from the use of tryptar in hemothorax are encouraging. Tryptar can be given by thoracentesis but it is believed that

better results will be more quickly achieved with closed catheter drainage with suction. The accumulation of large amounts of fluid in the pleural cavity from proteolysis after the injection of tryptar may cause a shift of the mediastinum and cardiorespiratory embarrassment. This complication can be easily avoided by the use of a catheter. The heavier sediment in the pleural space can often be washed out with physiologic saline through the catheter before the next treatment with tryptar. The best results from the enzyme will be obtained when treatment is started immediately after hemorrhage has stopped. If organization of the clot has started, it is increasingly difficult to obtain liquefaction because the enzyme does not affect living cells. Enzymatic treatment, nevertheless, may occasionally succeed despite delay. Treatment is given at least twice a day since a considerable portion of enzymatic activity is lost within four hours. The catheter is clamped for about four hours to permit digestion after which suction is re-established. The duration of treatment is guided by the temperature curve, the color of the aspirated fluid and repeated roentgenograms of the chest. The body temperature usually returns to normal when the blood has been removed from the pleural cavity. The persistence or recurrence of fever when only serous fluid is obtained should arouse suspicions of loculated blood or pus. Tryptar should be stopped when the aspirated fluid becomes serous unless loculations are present. Repeated roentgenograms of the chest are helpful in determining whether free fluid or loculations of fluid are present.

Wounds of the lung are sealed by fibrin in the normal process of repair and therefore the creation of bronchopleural fistula from the use of tryptar is possible. This complication has not been seen.

Benedryl was given to these patients receiving tryptar to decrease the possibility of allergic reaction to the enzyme. A histamine-like response to the enzyme was not seen.

The chosen chemotherapeutic and/or antibiotic agents should be given orally or parenterally before the results of culture of the aspirated fluid are known because all traumatic hemothoraces are potentially or actually infected. The agent may be changed when the result of the culture is learned.

The principles of treatment of pyogenic empyema are essentially those of hemothorax. A thick exudate may necessitate the use of tryptar more frequently than twice a day. The proteolytic action of the enzyme on the pleural surfaces will permit better contact and more efficient action of the selected antibacterial drug. Loculations will be broken down and the enclosed bacteria opened to the chosen drug. A bronchopleural fistula in a patient with a pyogenic empyema is not a contraindication to the use of tryptar. If necessary, however, additional surgical procedures to obliterate the bronchopleural fistula, should be done.

Tuberculosis is not a contraindication to the use of tryptar. The thick pus in the empyema cavity is converted into thin material which lends itself to ready aspiration. Care must be taken when tryptar is used in tuberculous empyema in the presence of a bronchopleural fistula since the

thin pus may be aspirated into other portions of the lungs. A thick pleura, which becomes well organized and is relatively avascular, does not lend itself to proteolysis. Tryptar may be tried in such instances since, although a complete debridement may not be affected, the pleural cavity will be prepared for manual decortication.

### SUMMARY

Tryptar provides the surgeon with another excellent therapeutic agent for the treatment of intrathoracic diseases. Fibrin is digested without harm to living tissues. Blood and pus are liquified and can be more easily removed. The excellent results obtained from the use of tryptar in this small series of patients with intrathoracic diseases suggests that further trial be given to the use of the enzyme in similar conditions.

### RESUMEN

El triptar proporciona al cirujano un excelente medio terapéutico para el tratamiento de las afecciones intratorácicas. La fibrina es digerida sin daño para los tejidos vivos. La sangre y el pus son licuados y pueden mas facilmente extraerse. Los excelentes resultados obtenidos del uso del triptar en esta pequeña serie de enfermos con enfermedades intratorácicas sugiere que se use mas esta enzima en condiciones similares.

### RESUME

Le "tryptar" donne au chirurgien une nouvelle possibilité thérapeutique excellente pour le traitement des affections intra-thoraciques. La fibrine est digérée sans créer le moindre dommage aux tissus vivants. Le sang et le pus sont liquifiés et peuvent être retirés beaucoup plus facilement. Les excellents résultats qui ont été obtenus par l'usage du "tryptar" sur un petit nombre de malades atteints d'affections intra-thoraciques que les auteurs ont suivis, font penser que des essais doivent être poursuivis dans des conditions comparables.

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# A Study of the Effects of Physiotherapy in Chronic Hypertrophic Emphysema Using Lung Function Tests\*

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Treatment of cases of chronic hypertrophic pulmonary emphysema has been generally regarded as a rather hopeless and unrewarding task. Apart from the use of antibiotics, oxygen and postural drainage where necessary the mainstay of rehabilitation has been the application of breathing exercises. These by focussing attention on expiration with special instruction in the use of abdominal muscles allegedly improve ventilation and diminish the state of hyperinflation of the lungs.<sup>1,2</sup> While it has been our experience that most patients claim to be benefitted by this form of treatment, clinical objective improvement is only rarely apparent to the unbiased observer. It seemed possible that the new hope engendered in the subject of a chronic rather hopeless incapacitating disease by the daily attention and implied optimism of the physiotherapist, might account in some measure for the patient's claims of improvement. Though it is part of the physician's function to engender this optimistic frame of mind it is also extremely important to know whether the treatment is in fact producing any real physical benefit. It was felt that this might be definitely established by the application of a group of physiological tests of lung function to a series of emphysematous subjects to see whether improvement in function could be recorded.

It was also felt that the usual form of breathing exercise might with advantage be augmented by the electrical stimulation of the abdominal and thoracic muscles during the expiratory phase. If, by electrical stimulation, the normal expiratory force could be increased it was hoped that the state of hyperinflation, characteristic of emphysema, might be diminished and improved ventilation might result. Accordingly two groups of emphysematous subjects were selected and studied before and after treatment by means of lung function tests. Treatment in the first group consisted of simple breathing exercises and in the second group of breathing exercises augmented by electrical stimulation during expiration. The object of this paper is to describe the results of these two experiments.

## *Material and Methods:*

Fifteen subjects with varying degrees of disability resulting from chronic emphysema were selected on clinical grounds. Radiological confirmation of the diagnosis was obtained in all cases.

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TABLE I

No.	Sex	Age	CLINICAL DATA				Blood Pressure	INVESTIGATIONS			
			Asthma	Bronchitis	Previous Heart Failure	Dyspnoea	Cyanosis	Hb. (gms. pct.)	P.C.V. (c.mm. pct.)	Electro-cardiogram	Alkali Reserve Vols. Pct.
1	M	39	0	+	+	+	+	17.6	52	R.V.+	66
2	M	56	0	+	0	++	+	17.8	-	Normal	-
3	M	56	+	+	0	+	+	16.9	58	R.V.+	61
4	M	52	0	+	0	+	0	17.2	-	-	60
5	M	67	0	0	+	+++	+	20.5	59	R.B.B.B.	67
6	M	60	+	+	0	++	+	20.2	56.8	R.V.+	62
7	M	38	0	+	+	+++	+	20.2	-	R.V.+	-
8	M	52	+	+	0	+	+	16.4	47	R.V.+	60
9	M	75	0	+	0	+	0	14.4	42	-	49
10	F	40	+	+	0	++	+	17.5	-	Normal	60
11	M	65	+	+	+	+	+	15.8	49	Normal	56
12	M	52	0	+	+	+++	+	17.8	55.5	R.V.+	-
13	M	42	0	+	+	+	+	16.2	56	-	59
14	F	55	+	+	0	+	+	16.2	51	Normal	58
15	M	62	+	+	0	++	+	18.8	58	R.V.+	63

TABLE II  
THE EFFECT OF BREATHING EXERCISES ON LUNG FUNCTION

Patient	Duration of Treatment (Days)	Measurements Expressed as Percentage of Predicted Value											
		Vital Capacity			Maximum Breathing Capacity			Total Capacity					
		Before	After	Pct. Change	Before	After	Pct. Change	Before	After	Pct. Change			
1	13	54	71	+32	43	70	+63	115	134	+17			
2	20	63	52	-18	76	47	-38	110	101	- 8			
3	18	74	77	+ 4	77	75	- 3	122	121	- 1			
4	20	81	75	- 7	56	72	+29	153	151	- 1			
5	20	64	45	-30	44	56	+27	141	144	+ 2			
6	21	80	82	+ 3	54	48	-11	124	133	+ 7			
7	46	65	63	- 3	141	109	-23	121	110	- 9			
8	30	64	76	+19	60	51	-15	127	127	0			
9	23	103	97	- 6	114	90	-21	150	139	-17			
10	24	89	67	-42	85	74	-13	144	131	- 9			
Average	23.5	73.7	70.5	- 4.8	75	69	- 1	130.7	129.1	- 1			
Normal Mean $\pm 2SD$		73			79			140					

TABLE II (Continued)  
THE EFFECT OF BREATHING EXERCISES ON LUNG FUNCTION

Patient	Functional Residual Capacity —				Percentage of Lung Volume —				Mixing Index —				Subjective Improvement
	Before	After	Pct. Change	Before	After	Pct. Change	Before	After	Before	After	Pct. Change	Before	
1	78	73	- 6	61	56	- 8			10	10	0		Marked
2	74	79	+ 7	62	64	+ 3			17	14	- 2		Moderate
3	74	72	- 3	56	50	-11			21	20	- 5		Nil
4	77	78	+ 1	64	63	- 2			21	18	-14		Marked
5	86	87	+ 1	69	72	+ 4			21	28	+33		Marked
6	73	76	+ 4	55	56	+ 1			18	12	-33		Moderate
7	77	72	- 6	58	57	- 2			13	11	-15		Moderate
8	78	77	- 1	61	52	-15			27	35	+26		Moderate
9	70	73	+ 4	53	52	- 2			28	23	-18		Nil
10	77	71	- 8	60	61	+ 1			16	10	-25		Moderate
Average	76.4	75.8	-0.7	59.9	58.3	-3.5			19.2	18.1	-3.5		
Normal Mean	67			38					22.3				

TABLE III  
THE EFFECT OF FARADIC MUSCLE STIMULATION OF LUNG FUNCTION

Patient	Duration of Treatment (Days)	<i>Measurements Expressed as Percentage of Predicted Value</i>									
		Before	After	Pct. Change	Before	After	Pct. Change	Before	After	Pct. Change	Before
3	22	76	79	+ 4	84	88	+ 5	121	118	- 2	118
5	22	61	62	+ 2	38	44	+16	152	141	- 7	141
6	17	881	80	- 1	47	54	+15	123	124	+ 1	124
8	18	67	64	- 4	62	60	- 3	127	127	0	127
11	18	87	103	+18	92	100	+ 9	115	107	- 6	107
12	15	45	60	+33	50	66	+32	104	115	+11	115
13	24	81	89	+10	68	80	+18	111	116	+ 5	116
14	19	96	70	-27	140	103	-26	136	119	-13	119
15	20	37	37	0	65	54	-17	113	110	- 2	110
Average	17.6	70	71.6	+ 3.9	71.8	72	+ 6.5	122	120	-15	120
Normal Mean	±2SD	73			79			140			

TABLE III (Continued)  
THE EFFECT OF FARADIC MUSCLE STIMULATION ON LUNG FUNCTION

Patient	Percentage of Lung Volume				Residual Volume				Mixing Index				Subjective Improvement
	Before	After	Pct. Change	Before	After	Pct. Change	Before	After	Before	After	Pct. Change	Before	
3	74	79	+ 7	50	58	+14	30	18	—	—	—40	—	Moderate
5	82	86	+ 5	69	69	0	25	21	—	—	—16	—	Marked
6	75	73	— 3	54	55	+ 2	13	18	—	—	+40	—	Slight
8	78	78	0	61	61	0	34	27	—	—	—20	—	Marked
11	65	69	+ 6	40	38	— 5	16	17	—	—	+ 6	—	Moderate
12	79	72	— 9	67	60	—12	22	22	—	—	0	—	Marked
13	74	77	+ 4	44	42	— 5	21	25	—	—	+19	—	Moderate
14	70	81	+15	50	56	+12	40	19	—	—	—52	—	Marked
15	81	76	— 6	77	71	— 8	15	27	—	—	+80	—	Marked
Average	75.3	77	+2.1	57	56	—0.02	24	21.5	—	—	+16	—	
Normal Mean	67			38			22.3						

Clinical, electrocardiographic and haematological data are shown in Table I. Additional confirmation was obtained in all by the use of a group of lung function studies (Tables II and III).

The battery of tests used was made up as follows:

1) Spirometry was carried out before and after the administration of an antispasmodic drug (Iso-propyl noradrenaline: 5 mgm.). From this was calculated the vital capacity, maximum breathing capacity, inspiratory capacity and expiratory reserve volume, the first two being expressed as a percentage of the predicted value for the subject concerned.<sup>5</sup>

2) Functional residual capacity was measured by a closed-circuit constant volume apparatus of the type originally used by McMichael<sup>3</sup> with adaptations.<sup>4</sup> Residual volume was calculated by subtracting the expiratory reserve volume from the value for functional residual capacity obtained above.

3) Total lung capacity was calculated and compared with the predicted value.<sup>5</sup>

4) Mixing efficiency was estimated using the index advised by Bates and Christie<sup>6</sup> with the difference that whereas Bates and Christie adjusted all their results so that the top normal was 100 per cent, in this series the figure was calculated without this adjustment.

5) Oximetric studies (using a Waters-Conley absolute reading oximeter) to show resting arterial oxygen saturation, and the changes in saturation following on effort ( $\pm 20 \times 9$  inch steps in one minute), maximum hyper-ventilation (1 minute) and inhalation of 100 per cent oxygen until the maximum rise in saturation had taken place.

In addition, a full blood count and an estimation of the alkali reserve were carried out in most patients.

It will be seen that most of the tests of function used (1-4 above) were measurements of ventilatory capacity<sup>5</sup> while the oximetric studies might be considered to test both ventilatory and alveolo-respiratory capacity together. It was considered that in so far as both forms of physiotherapy employed were primarily designed to improve ventilatory function, improvement could be adequately studied by the battery described above without the need of further information concerning alveolo-respiratory exchange.<sup>7</sup>

Cases were only selected for study after the maximum improvement possible had been obtained by the use of other methods of treatment such as antibiotics, antispasmodics and oxygen.<sup>8</sup> Their respiratory function was then studied for an average period of 15.5 days before physiotherapy was commenced. This allowed time for subjects to become accustomed to the tests and for the improvement associated with practice to be eliminated. After this period of pre-treatment study one of the two forms of physiotherapy to be assessed was commenced. Breathing exercises were carried out on three days per week with instructions to practice twice daily in between visits. Especial emphasis was laid on the expiratory phase, on improvement of diaphragmatic movement and on general relaxation. In the second form of treatment (referred to hereafter as "Faradic muscle

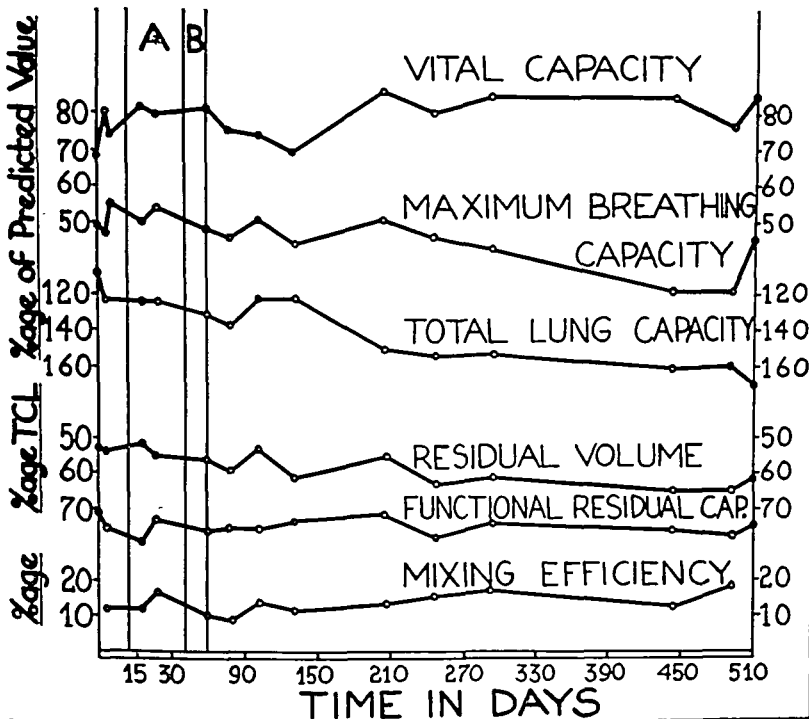
stimulation") normal breathing exercises were performed with expiration assisted by the use of faradic current applied to the chest and abdominal muscles in such a way as to produce firm contraction. The current was initiated by the patient with a press switch at the beginning of expiration.\* The onset of stimulation after the switch was pressed was gradual, rising to maximum within two seconds and was discontinued at the end of expiration by the patients releasing the switch. This treatment was carried out once or twice daily for a minimum period of an hour per day.

In all, the battery of tests described above was carried out 115 times on 15 subjects, each being studied for an average of 79.8 days (range 23-205 days) with an average of 6.1 complete studies per subject (range 3-10). One or other form of treatment was carried out for an average period of 28.5 days (range 13-62 days), function studies being carried out at approximately weekly intervals. Four subjects received both forms of treatment. This was only considered permissible when the first form of treatment had produced negligible changes in function tests.

#### Results:

The fluctuations in values obtained over a long period of observation are well illustrated in Figure 1, where the results of the successive studies on Case 1 are graphed with the scales arranged in such a way that a rise of the graph indicates deterioration and a fall improvement. It would

\*"The Electric Lung". Ludwig Schulmeister, Vienna.





appear that no significant effect has been produced by therapy, and that the case has followed a course of slow steady deterioration quite uninfluenced by the period of treatment.

For the purposes of comparison the values obtained in tests performed immediately before the commencement of the therapy were compared with the values obtained after a period of treatment lasting on an average 23.5 days (range 13-46 days), the duration of treatment being determined by such factors as the patient's enthusiasm and ability to spare the time. The change observed in each value is expressed as a percentage of the "before treatment" value, and in Tables II and III these results may be compared with the patient's subjective assessment of his own improvement.

Firstly it will be seen that all but two subjects (Nos. 3 and 9) claimed that while receiving breathing exercises they felt better and that their effort tolerance improved. In contrast, the majority of cases showed no significant change in measured values and the average percentage change for the whole group with each form of therapy can not be considered significant.

In the group receiving breathing exercises alone, only case 1 appears to have shown improvement in several values. Even in this case, however, the mixing index remained unchanged and the total lung capacity increased after treatment while the oximetric results appear to reflect deterioration (Table IV). In cases 2 and 10 there was deterioration in several values while it is impossible to detect a significant trend in any of the others.

In the group in whom breathing exercises were augmented by faradic stimulation (Table III) there was apparently significant improvement in case 12 and possibly significant improvement in some values in cases 11 and 13. In case 14 there was significant deterioration while in the rest no significant trend could be detected.

In two cases function studies were performed before and after a half-hour treatment by breathing exercises and faradic muscle stimulation. In neither was there any significant effect on vital capacity nor did treatment appear to reduce the state of inflation of the lungs in any way.

Thus far only values derived from lung capacity measurements and spirometry, and the mixing index have been considered. In none of the nine cases in whom the alkali reserve was measured before and after treatment was a fall of greater than three volumes observed. The oximetric results are recorded in Table IV. It will be seen that a significant rise (over 4 per cent<sup>9</sup>) in resting arterial oxygen after treatment was found in four subjects and a significant fall in five others of the 14 subjects in whom values were obtained before and after treatment. In only subjects 6 and 13 does the fall in arterial saturation after effort suggest significant improvement, while in others, notably cases 1, 2 and 12 actual deterioration is suggested. The changes produced by hyperventilation apart from case 12 in whom deterioration is suggested were surprisingly constant both before and after treatment.

TABLE IV  
ARTERIAL OXYGEN SATURATION BEFORE AND AFTER TREATMENT  
1) Treatment by Breathing Exercises

Case	— Resting Level —		— Fall on Effort —		— Hyperventilation —	
	Before	After	Before	After	Before	After
1	77	79	— 4	— 11	+ 5	+ 3
2	93	85	— 6	— 17	+ 4	+ 8
3	93	94	— 1	— 5	+ 4	+ 5
4	93		— 7		+ 1	
5	91	82	— 3	— 8	+ 4	+ 7
6	76	83	— 13	— 6	+ 10	+ 3
7	55*					
8	95		— 2			
9	84	87	— 3	— 2	0	0
10	93		— 22		+ 7	

2) Treatment by Faradic Muscle Stimulation

Case	— Resting Level —		— Fall on Effort —		— Hyperventilation —	
	Before	After	Before	After	Before	After
3	94	87	— 4	— 9	+ 5	+ 6
5	87	92	— 6	— 3	0	+ 2
6	81	76	— 10	— 13	+ 7	+ 10
8	87	95	— 4	— 2	+ 2	+ 5
11	95		0		+ 4	
12	82	73	— 3	— 12	+ 8	— 1
13	88	93	— 6	0	+ 7	+ 5
14	85	86	— 3	— 4	+ 9	+ 9
15	87	87	— 6	— 4	+ 6	+ 5

\* Direct measurement on van Slyke apparatus.

### Discussion

It is soon apparent to anyone who repeats respiratory function tests at regular intervals in emphysematous subjects that in many, a definite week to week fluctuation is apparent in the values obtained. This parallels approximately the patient's subjective state. Factors which are known to produce these fluctuations are the degree of bronchospasm, the degree of bronchial infection and the degree of heart failure. Every effort has been made to eliminate these factors as far as possible in this series. Cases with active asthma and those with symptoms of heart failure were excluded before the trial began. One subject who developed a flare up of bronchitis during treatment and deteriorated as a result was excluded as

was another who developed cardiac failure. However the tables and Figure I reflect that, as might be expected, considerable fluctuation occurred in some subjects.

To demonstrate the efficacy of a form of treatment in a group of subjects in a proportion of whom spontaneous deterioration and improvement is taking place it is necessary at least to show that during the course of treatment more cases improve than deteriorate. This we have failed to do. During the 19 courses of physiotherapy there appears to have been probable improvement recorded in two cases, possibly significant improvement in some values in two, and significant deterioration in three. It thus seems probable that the improvement recorded in certain cases was the result of natural fluctuation in the subject's condition rather than the result of therapy.

Lastly it is worthy of note that improvement was claimed by all of the three subjects in whom deterioration was demonstrated by lung function studies. We are not of course able to exclude the possibility that some aspects of lung function other than those assessed by our tests have been improved by treatment. It has seemed to us more likely, however, that the patient's claims of improvement are the result of an increased optimism and a subconscious desire to gratify those who have given him such close and careful attention during his period of treatment and study.

### SUMMARY

1) Respiratory function tests have been applied to 15 emphysematous subjects on several occasions until base line values have been obtained.

2) The patients have then been subjected to one of two forms of physiotherapy; either a course of breathing exercises or a course of breathing exercises augmented by electrical stimulation of chest and abdominal muscles during expiration. Function tests have been repeated and changes assessed.

3) In all, 19 studies were carried out on 15 subjects. Though all but two claimed to feel better after treatment, function studies suggested probable improvement in only two, possible improvement in two more, and deterioration in three. In the rest no definite change was observed.

4) It was concluded that no evidence of the efficacy of these procedures had been obtained and that the benefit claimed by the subject was more likely to be the result of his mental attitude than of true physical improvement.

*Acknowledgments:* We should like to thank Professor G. A. Elliott in whose Department this work was carried out, and the physicians of the hospital, in particular Dr. M. M. Suzman for giving us the opportunity of studying cases under their care. The cases treated by breathing exercises were supervised by Dr. T. Dreyer of the Department of Physical Medicine, Johannesburg General Hospital. Messrs. Protea Holdings, kindly lent the "Electric Lung".

### RESUMEN

1) Se han aplicado las pruebas funcionales a 15 enfisematosos en varias ocasiones hasta que la línea básica de valores se obtuvo.

2) Los enfermos han sido sujetos a una o dos formas de tratamiento fisioterápico, ya sea una serie de ejercicios respiratorios o una serie de los mismos, más la estimulación eléctrica de los músculos del tórax y del abdomen durante la expiración. Se repitieron las pruebas y se estimaron los cambios.

3) En total se hicieron 19 estudios en 15 sujetos. Aunque todos declararon que se sentían mejor después del tratamiento, los estudios funcionales sugirieron probable mejoría sólo en dos, posible mejoría en otros dos y empeoramiento en tres. En el resto no hubo cambio definido.

4) Se concluyó que no había evidencia de la eficacia de esos procedimientos y que el beneficio declarado por los enfermos, era más probablemente el resultado de su actitud mental que una verdadera mejoría física.

### RESUME

1) Les auteurs ont recherché les tests respiratoires chez 15 malades emphysemateux à de nombreuses reprises, avant d'obtenir des éléments de base solides.

2) Les malades ont ensuite été soumis à un ou deux modes de physiothérapie. On a utilisé soit une série d'exercices respiratoires isolés, soit une série d'exercices respiratoires auxquels a été associée une stimulation électrique du thorax et des muscles abdominaux au cours de l'expiration. Les épreuves fonctionnelles ont été alors répétées, et on a noté leurs modifications.

3) Dans l'ensemble, les 15 sujets ont fait l'objet de 19 études. A part deux d'entre eux, tous se sentirent mieux après le traitement. Néanmoins, l'étude fonctionnelle montre une amélioration probable chez deux d'entre eux seulement, une amélioration possible chez deux autres, et une aggravation chez trois d'entre eux. Pour tous les autres, aucune modification n'a pu être observée.

4) Les auteurs en concluent qu'il n'y a aucune preuve de l'efficacité de ce procédé, et que le bénéfice invoqué par les malades était plus d'ordre psychique que véritablement en rapport avec une amélioration physique.

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# Cor Pulmonale

## A Consideration of Clinical and Autopsy Findings\*

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Chronic cor pulmonale may be defined as hypertrophy of the right ventricle initiated by pulmonary hypertension. This follows increased resistance to blood flow within the lesser circulation as a result of parenchymal pulmonary disease, primary pulmonary arteriolar disease, or marked deformity of the thoracic cage. The existence of such heart disease may be recognized clinically in the presence of signs of failure of the right ventricle, or in the absence of frank failure by a combination of history, physical findings, x-ray and electrocardiographic evidence. Post mortem examination reveals right ventricular hypertrophy in a certain percentage of patients in whom clinical diagnosis has not been established.

In 1783, Senac remarked on cardiac enlargement in asthmatics. Louis, in 1830, stated that enlargement of the heart occurred in all of the cases he had seen die of emphysema who also had edema. Budd, in 1840, stressed the reduction in capillary circulation of the lungs in emphysema leading to obstruction of circulation through the pulmonary arteries, and finally to dilatation of the right heart and edema "so frequently met with in emphysematous persons". Laennec mentioned hypertrophy and dilatation of the heart and dilatation of the pulmonary artery as a sequel to emphysema. Sibson, in 1848, described autopsies on patients with emphysema dying in congestive failure with marked hypertrophy of the right ventricle.<sup>1</sup> In the 1920's and 1930's there was considerable controversy about the frequency and the pathogenesis of cor pulmonale. White and Brenner,<sup>2</sup> in 1933, remarked on the rarity of cor pulmonale. At present exact figures of the incidence of chronic cor pulmonale are lacking, but Sprague<sup>3</sup> remarks on its relative infrequency in the United States. He quotes the findings of White and Jones who reported in 1928 an incidence of 0.9 per cent in a series of 2,314 cases of organic heart disease in New England, and a report by White of 25 well marked cases of chronic cor pulmonale in 4,000 post mortem examinations at the Massachusetts General Hospital from 1932 to 1942.

Several articles reveal widely varying figures on the incidence of cor pulmonale, and as might be expected a quite high percentage is reported where the work is based on post mortem findings in patients with long standing severe pulmonary disease. Griggs, Coggin and Evans,<sup>4</sup> in a study of cor pulmonale in 1937, reviewing autopsy protocols of 18,000 consecutive autopsies, found the highest incidence of right ventricular hypertrophy in silicosis. Fifty-two per cent of 24 patients with silicosis showed right ventricular hypertrophy, with failure in 50 per cent. In 45 cases of pure

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emphysema, right ventricular hypertrophy was found in 28.9 per cent, with failure in 22 per cent. The hearts of patients with pulmonary tuberculosis showed right ventricular hypertrophy in 3.7 per cent, with definite failure in 1.8 per cent of the 1,470 cases. In 41 cases of tuberculosis with associated pulmonary lesions, particularly pneumoconiosis, 36.6 per cent had right ventricular hypertrophy. Nemet and Rosenblatt,<sup>5</sup> in 1937, found exclusive hypertrophy of the right ventricle in 34 per cent of 71 cases of pulmonary tuberculosis. Kountz, Alexander and Prinzmetal,<sup>6</sup> in 1936, who separated and weighed the right and left ventricles of 17 patients with marked emphysema, found hypertrophy of the right ventricle in 10 of 17 cases, with hypertrophy of both right and left ventricle in most of these cases. Scott and Garvin,<sup>7</sup> in 1941, reviewed a series of 6,548 autopsies at the Cleveland City Hospital to determine the incidence of primary right heart hypertrophy (excluding congenital defects and regardless of the presence or absence of failure, using the thickness of the right ventricle as a criterion). In this series there were 790 who died of heart disease, of which 50, or 6.3 per cent, seemed to be cor pulmonale. Spain and Handler<sup>8</sup> reviewed 60 cases of cor pulmonale. In their series the leading etiologic factor was tuberculosis, followed by asthma, bronchiectasis and emphysema. A fairly large number, nine of the 60, had primary pulmonary arteriolar sclerosis. The figures on incidence of cor pulmonale in tuberculosis vary from approximately 4 to 40 per cent. Higgins<sup>16</sup> reported that about 30 per cent of all tuberculosis patients coming to autopsy at the Green Lake Sanitarium showed evidence of right heart failure.

The author's experience indicates that chronic cor pulmonale is a frequent and often overlooked form of heart disease. A large percentage of our medical patients are sent to Arizona for climatic relief of respiratory disease. These patients have generally experienced progressive shortness of breath with onset in the late 40's or early 50's with usually no prior history of asthma, pulmonary infection, or occupational exposure to dusts. The chief abnormal physical finding is marked emphysema. After two or three years of progressive dyspnea despite medical treatment they are either sent or come of their own volition to Arizona for climatic relief. In these patients, as well as in our tuberculous patients, cor pulmonale is a prominent feature.

From November 5, 1948, to October 29, 1951, a total of 174 autopsies were performed. In 106 of these a significant degree of cardiac abnormality was found, but not all of them had been diagnosed clinically as having heart disease. Of the 106 patients with heart disease 54 or slightly over 50 per cent were considered to have cor pulmonale from the criteria mentioned below. The most common cardiac abnormalities at post mortem, aside from cor pulmonale, were those secondary to arteriosclerosis and hypertension.

The pathological diagnosis of cor pulmonale was based on the presence of right ventricular hypertrophy, the absence of significant intrinsic cardiac disease, and the presence of sufficient pulmonary disease to act as an etiological factor. Right ventricular thickness of 5 mm. or over was regarded

as evidence of right ventricular hypertrophy. In two cases a right ventricle which measured 4 mm. in thickness was regarded as hypertrophied. In these cases the left ventricle was only 10 mm. in thickness. Hypertrophy of the papillary muscles and trabeculae carnae of the right ventricle was regarded as significant in determining abnormal degrees of right ventricular hypertrophy. Patients with hypertrophied right ventricles who also had coronary disease, or systemic hypertension with left ventricular hypertrophy, were not regarded as having cor pulmonale. Thickness of the right ventricle in this series with cor pulmonale varied from 4 to 15 mm., and the thickness of the left ventricle from 10 to 20 mm. In one a 20 mm. left ventricular thickness was associated with a 10 mm. thickness of the right ventricle. The thickest right ventricle, 15 mm., was associated with a left ventricular thickness of 18 mm. The average thickness of the right ventricle was 7.3 mm., and the average thickness of the left ventricle was 14.4 mm. The heart weight varied from 260 to 510 grams. Most of the hearts were over 400 grams in weight. In patients with arteriosclerotic and hypertensive heart disease, despite marked thickness of the left ventricle, the right ventricle was not proportionately increased in thickness. Thus, for example, a 23 mm. left ventricular thickness might be associated with a right ventricular thickness of 6 or 7 mm. The state of the heart at the time of death, whether in systole or diastole and the amount of cardiac dilatation, makes a considerable difference in the measured thickness of the ventricle. The point of measurement also makes considerable difference.

Several studies of cor pulmonale have been carried out by investigators who weighed the left and right ventricles separately. Numerous authors have remarked on the fairly consistent presence of left ventricular hypertrophy in cor pulmonale and have given various explanations for this finding. The explanation of Parkinson and Hoyle<sup>1</sup> is that the left ventricular hypertrophy is due to coincidental hypertension. This does not explain the finding in any of our cases, as none of them had a significant degree of systemic hypertension. Other explanations of the presence of left ventricular hypertrophy include anoxia as the significant mechanism causing left ventricular hypertrophy, and the explanation of Scott and Garvin<sup>7</sup> that the arrangement of muscle fibers of the right and left ventricles are such that hypertrophy of one ventricle necessitates a concomitant hypertrophy of the other.

Table I itemizes some of the data from our post mortem statistics. Slightly over 50 per cent of our patients with pulmonary tuberculosis and with other chronic pulmonary disease (chiefly emphysema) were found to have cor pulmonale. It should be noted that over 90 per cent of our deaths were autopsied during the period covered by this report. In this series of patients where pulmonary emphysema seemed to be more marked than the amount of tuberculosis, the case is included as other pulmonary disease rather than tuberculosis. It should be noted that all of the tuberculous patients with cor pulmonale had considerable emphysema. With the exception of four tuberculous patients who died following surgery or pulmonary hemorrhage, all of the tuberculous patients with cor pulmonale

died of pulmonary insufficiency or a combination of cardio-pulmonary insufficiency. Two with emphysema and cor pulmonale died of hemorrhage from gastric ulcers, and one died following surgery for traumatic intra-abdominal injuries. All of the remainder died of pulmonary insufficiency or a combination of cardio-pulmonary insufficiency. Only 13 of the 54 who showed definite right ventricular hypertrophy at autopsy were noted as being in clinical failure before death. The presence of cardiac failure could not be definitely equated with the amount of right ventricular hypertrophy, a finding analagous to that seen in systemic hypertension.

Of the 54 found to have chronic cor pulmonale at autopsy, a clinical diagnosis of cor pulmonale was made in only 21, and of the group of 54 only 13 were in clinical cardiac failure before death.

TABLE I: POSTMORTEM INCIDENCE OF COR PULMONALE  
AND ETIOLOGICAL FACTORS CONCERNED

Whipple VAC, November 5, 1948, to October 29, 1951

	Number Autopsied	Pct. of Autopsies	Pct. of Group	Pct. of Total Cor Pulm.
All autopsies	174	100	100	
Number with heart disease	106	61	100	
Number with cor pulmonale	54	31	51	
Number with pulmonary tuberc.	62	36	100	
Tuberc. cases with cor pulmonale	32	18	51	
Pulmonary diseases not tuberc. (Chiefly emphysema)	41	24	100	
Non-tuberc. with cor pulmonale	22	13	54	
Clinical diagnosis of cor pulmonale	21	12		38
Cor pulmonale patients in clinical cardiac failure	13	7		25

In the patient with obvious right heart failure with edema, distended neck veins, ascites, hepatomegaly and cyanosis, the diagnosis of cor pulmonale may be made readily. The diagnosis of enlargement of the right heart prior to the onset of failure is important from the standpoint of therapy and prognosis and it is a diagnosis not too readily made. Physical examination alone usually is of limited value. In the absence of failure the heart size is likely to be normal, and enlargement of the various portions of the heart cannot be determined by physical examination in the patient with severe chronic pulmonary disease. The presence of an accentuated pulmonary second sound and a forceful sub-xiphoid pulse should be viewed with suspicion. In many cases the heart sounds are so muffled by emphysema as to be inaudible except in the sub-xiphoid region. In the absence of cardiac failure circulation time is normal. The cardiac rhythm is usually normal whether the patient is in failure or not. In only one of the cases in this series was there an abnormal rhythm, an auricular flutter in a case with cor pulmonale and tuberculous pericarditis in failure. In this



patient a catheter had been placed in the pericardial cavity believing it to be the pleural cavity, and lavage with azo-chloramide had been carried on.

The venous pressure may be elevated in emphysema in the absence of failure, or may be normal at rest and rise on exercise. This increase in venous pressure in the absence of cardiac failure has usually been ascribed to an increase in intra-pleural pressure.

The x-ray and electrocardiogram are of great value in the diagnosis of cor pulmonale prior to the onset of failure. X-ray findings are of limited value in those patients with advanced tuberculosis or silicosis which renders evaluation of the cardiac silhouette difficult, but are of considerable value in patients with emphysema. Enlargement of the pulmonary arteries is frequent, and enlargement of the pulmonary conus is frequently the first indication of cardiac enlargement. Enlargement of the body of the right ventricle is less frequently seen. The transverse diameter of the heart usually is enlarged only in the presence of failure. Angiocardiography in emphysema is reported as showing a high percentage of right ventricular dilatation.<sup>10</sup> The use of a barium swallow to outline the esophagus is of value in differential diagnosis of mitral disease and its accompanying left auricular enlargement. Fluoroscopy in primary pulmonary vascular disease is characterized by a large pulsating pulmonary artery and right ventricular hypertrophy.

With the routine use of 13 leads, the electrocardiogram is of great value in the diagnosis of right ventricular hypertrophy. Our accuracy in diagnosing cor pulmonale has increased since we have been taking routine electrocardiograms of tuberculous patients and medical patients with chronic lung disease using the three standard leads, unipolar limb leads, V<sub>3</sub>R and V<sub>1</sub>-V<sub>6</sub>. The characteristic findings consist of high R-waves in leads over the right precordium, and deep S-waves in leads over the left precordium; depression of the S-T intervals and T-waves inversions over the right side of the heart are also of considerable diagnostic value. A high, peaked P-wave in leads 2 and 3 and the left leg lead, and the presence of a Q-wave and high R-wave in the right arm lead, are also of value in determination of cor pulmonale. Due to the markedly vertical position of the heart with clockwise rotation, the chief findings may be low to absent R-waves in chest leads V<sub>1</sub>-V<sub>6</sub>, with R-waves becoming more prominent as the leads are shifted one or two interspaces below the conventional levels. Electrocardiographic changes which would be equivocal if seen in a single curve become of diagnostic value when compared with previous records. Additional exploratory leads over the right chest may be of value in cases where right ventricular hypertrophy is suspected and the orthodox leads are not diagnostic. It has been our experience that the electrocardiogram will show evidence of right ventricular hypertrophy before it can be demonstrated by x-ray inspection. In a certain proportion of patients definite right ventricular hypertrophy will be found at post mortem in whom electrocardiogram and x-ray findings are within normal limits and physical examination has not revealed definite evidence of cardiac involvement.

The intensive studies of cardio-respiratory physiology<sup>11-15</sup> in recent years have focused attention on the circulatory and cardiac changes seen in chronic pulmonary disease, and have placed therapy on a more rational basis. The importance of acute anoxia in causing pulmonary hypertension has been emphasized. In the patient with chronic pulmonary disease the pulmonary vascular bed is reduced by the anatomic lesions, and anoxia and polycythemia further increase the disproportion between pulmonary blood flow and capacity of the pulmonary vascular bed. In the past, and as recently as 1951,<sup>3</sup> the grave prognosis of cardiac failure in chronic cor pulmonale has been stressed, but in our experience failure of this type may respond well to treatment consisting of the usual measures of rest, digitalization, salt restriction, mercurial diuretics and oxygen. Phlebotomy is used if the hematocrit is over 60 per cent, and antibiotics are used at the slightest suspicion of pulmonary infection. Bronchodilators (particularly ephedrine) are of value and are continued after the attack of failure is relieved. Potassium iodide is used as an expectorant.

#### SUMMARY

1) Autopsy findings from November, 1948, to October, 1951, at this hospital demonstrated an incidence of right ventricular hypertrophy of 50 per cent in patients with pulmonary tuberculosis and chronic emphysema.

2) Chronic cor pulmonale is much more frequently seen at autopsy than the clinical diagnosis would indicate. Awareness of the situation in which cor pulmonale is particularly prevalent, and the use of appropriate diagnostic study, should make clinical appraisal of the patient more accurate and lead to more effective treatment and more intelligent prognosis.

#### RESUMEN

1) Los hallazgos de autopsia de Noviembre de 1948 a Octubre de 1951 en este hospital, demuestran la frecuencia de la hipertrofia ventricular derecha que es de 50 por ciento de los enfermos con tuberculosis pulmonar y enfisema crónico.

2) El corazón pulmonar agudo es mucho más frecuente encontrado en la autopsia de lo que el diagnóstico clínico haría suponer. Una alerta sobre las situaciones en las que el cor pulmonale es particularmente prevaleciente y el uso de medios adecuados de diagnóstico, permitirán una estimación más exacta del estado clínico del enfermo así como conducirían a un tratamiento más efectivo y a un pronóstico más inteligente.

#### RESUME

1) Les auteurs rapportent les constatations faites au cours des autopsies pratiquées dans leur service d'hôpital de 1948 à octobre 1951. Elles montrent la fréquence de l'hypertrophie ventriculaire droite que se vérifie chez 50% des malades atteints de tuberculose pulmonaire et d'emphysème chronique.

2) Le coeur pulmonaire apparaît bien plus fréquemment à l'autopsie que ne le laisserait prévoir le diagnostic clinique. Celui-ci devrait être plus facilement porté compte tenu de la fréquence du coeur pulmonaire et de

l'utilisation des moyens d'investigation appropriés. Ainsi pourraient être établis un traitement plus efficace et un pronostic plus rationnel.

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## Comments on Systemic Sarcoidosis

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The precise incidence of sarcoidosis is not known. It has been estimated that over 1,000 cases have been reported by 1948.<sup>1</sup> Between 1936 and 1948, 25 cases were seen in Pennsylvania Hospital and between 1947 and 1952, 21 cases were seen in the Jefferson Hospital. Among some 628,000 residents of Philadelphia of all ages, sex and color examined roentgenologically for tuberculosis during the past 10 years by the Philadelphia Tuberculosis and Health Association slightly over 2 per 100,000 presented roentgenologic findings compatible with sarcoidosis, later proved by biopsy. Although the disease is world-wide in distribution, it is more prevalent among the rural folk living in the temperate zone. In the United States, for some reason, the disease is more common in the southeastern portion, predominantly in the rural rather than in metropolitan areas. In an epidemiologic study of 226 cases of sarcoidosis in military personnel by Michael et al.,<sup>2</sup> 88 per cent came from the southern United States. This was true for both Negro and white groups. Even among the Negro group those born in the South showed an incidence of 25 per 100,000 inductees, as compared to an incidence of 1 per 100,000 in those with Northern birth-place and 6 per 100,000 in those from the west. This suggests that whatever the etiologic factor may be, it appears more concentrated in the southern United States. The disease has been noted in Japan, Australia, South America and South Africa. In Europe the Scandinavian countries reported most of the cases.

People of all ages are affected. Predominantly, however, it appears to be a disease of early adult life between the third and fourth decades. In the United States there is no doubt that the condition is more prevalent in Negroes; in some studies the incidence in Negroes was 16 times as great as in whites.

This disease was first described in 1875 by Hutchinson.<sup>3</sup> The patient was a woman named Mortimer, aged 65. The lesions consisted of a number of patches on her cheeks and back of her upper arms. The patches were raised and sharply defined on skin otherwise healthy. They were red and not ulcerated, but showed some scales. Gradually the lesions spread over the entire face. He named the condition "Lupus Vulgaris Multiplex Non-Ulcerans et Non-Surpiginosus". Fourteen years later Besnier reported the second case.

Boeck<sup>4</sup> of Norway reported (1894) a 36-year-old police officer in good health except for skin disease on the brow, spreading to other parts of

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the face, limbs and trunk. He removed two skin nodules each about the size of a pea and described the histologic features of sarcoid. Curiously enough, the autopsy specimens from this same patient were examined in 1947; no evidence of sarcoid was found<sup>5</sup> anywhere. The patient died at the age of some 80 years of hypernephroma. Heerfordt first noted fever, uveitis, parotitis and paralysis of the facial nerve. Bruins Slot suggested that uveoparotid fever was a form of sarcoidosis. Schaumann noted the disease was primarily a systemic condition and Jungling first noted involvement of the bones of the hands. The term sarcoid proposed by Boeck is derived from two Greek roots meaning "flesh" and "form".

The organs most frequently involved are lymph nodes, lungs, liver, spleen and skin. Involvement of the heart, small bones of the hands, stomach, intestines, kidneys, bladder, pituitary and thyroid glands, eyes, voluntary muscles and central nervous system has been noted.

Regardless of the tissue or organ involved, the basic lesion is always the same. It is a sharply delineated granuloma composed of uniform polyhedrol cells with abundant acidophilic cytoplasm and large, ovoid, vesicular nuclei. As the lesion matures, a narrow rim of two or three layers of fibroblasts encircle it while epithelioid cells elongate and become concentrically arranged. Regression by fibrosis then occurs, beginning as a fibrotic process between and around the individual granulomas. The fibrous tissue rapidly becomes compact, hyalinizes and forms a dense scar in which only a suggestion of the previous tubercle remains. Numerous giant cells are found within these lesions.

Some giant cells carry inclusion bodies, the Schaumann body and the spiculated body of "asteroids". Schaumann bodies are found in 3 per cent and "asteroids" in 2 per cent. Neither of the inclusion bodies is specific of this disease. Schaumann bodies are seen in the lymph nodes of lymphopathia venereum and in giant cells in the lymph nodes draining an area of regional ileitis. Asteroids occur in tuberculosis, leprosy, histoplasmosis, schistosomiasis and lipoidal granuloma. Occasional vasculization occurs in the giant cells.

Necrosis in sarcoidosis has been described as "fibrinoid" and is strongly eosinophilic. A few intact lymphocytes may occur about the periphery of the necrotic area, but otherwise the necrosis is usually acellular. Total absence of cells and cellular debris with fibrillar zones of necrosis distinguishes this from the caseation of tuberculosis. In no case of sarcoidosis has *Mycobacterium tuberculosis* been found.

Enlarged lymph nodes, cough, dyspnea, weight loss, skin manifestation, low grade fever, malaise and weakness, deformity of the hands when the bones are involved, conjunctivitis, poor vision, and facial paralysis are the symptoms and signs. Quite frequently the condition is suspected following roentgenological examination of the chest prior to employment. In such cases, despite pronounced changes in the lungs, the person may not have any symptom.

The cause of sarcoidosis is still unknown. Whether the disease is an atypical form of tuberculosis is one of the most controversial issues in

medicine. That it is some form of tuberculosis is more generally accepted in Europe than in America. The strongest evidence against tuberculosis as an etiologic factor is that in addition to the usual negative reaction to the tuberculin test, in no unequivocal case of sarcoidosis was *Mycobacterium tuberculosis* ever found. *Mycobacterium leprae*, *Treponema pallidum*, Protozoa, viruses, fungi, helminths, beryllium, foreign bodies such as paraffin, crystalline material, silica, soil, silk,<sup>6</sup> wool and others and certain hyperergic states of the victim with arteriolar lesions, as well as neoplastic origin and collagen disease are sometimes considered as possible causes.

Regarding some of the methods of diagnosis, a punch biopsy of the liver by means of Vim-Silverman needle and lung biopsy may be mentioned. Liver biopsy is of particular importance when the skin and superficial lymph nodes are not involved. The chief objections to needle biopsy are that serious, and occasionally fatal, complications may follow and that the small samples of tissues obtained may fail to include lesions, although actually present in the liver. The dangers are negligible, provided the procedure is carried out skillfully and precautions are taken in the selection and postoperative care of patients. There was no fatality in 650 biopsies done by Klatskin.<sup>7</sup> He showed close resemblance in morphology between the hepatic lesions of sarcoidosis and those of tuberculosis, erythema nodosum and brucellosis. Granulomata in tuberculosis and brucellosis exhibited greater incidence of caseation and necrosis of the tissues, and inflammatory reaction of the tissues surrounding the granulomata, but most of the lesions could not be differentiated on histological appearance alone.

Needle biopsy of the liver has definite value in confirming the diagnosis of sarcoidosis, despite the uncertainties due to the resemblance of the tissue reactions in sarcoidosis with that seen in other diseases. In Scandinavia biopsy of the tonsillar tissues is popular.

Lung biopsy apparently is a safe procedure. Under local anesthesia a small incision is made in the anterior surface of the thorax, usually between the third and fourth ribs at the anterior axillary line. Then the patient is made to inhale oxygen under positive pressure. In so doing the increased intrapulmonary pressure forces the lung to protrude through the incision. That part of the lung is tied and incised. Tissue is fixed in formalin and stained in the usual manner and examined. In over 24 pulmonary biopsies done during the past year in Jefferson Hospital by Allbritten, there was no case of pneumothorax, empyema or other complication. Patients were able to leave the hospital in 24 hours, in perfect comfort.

The so-called Nickerson-Kveim test, which is an intradermal test using 0.15 cc. of suspension of sarcoid nodules in isotonic solution of sodium chloride, is again a controversial one. In some hands this test has been satisfactory; for example, it was found to be 80 per cent positive in the series studied by Siltzbach. On the other hand, in Jefferson Hospital the test has been unreliable and, as a matter of fact, it is not used as a routine procedure in the study of sarcoidosis. One of the disadvantages of this test is that even in a proved case of sarcoidosis a definite reaction does not

take place for weeks to months. Sones<sup>8</sup> carried out studies on immunological reactions in sarcoidosis on 38 patients and found that patients with sarcoidosis reacted less often than controls, not only to tuberculin but also to pertussis agglutinin, mumps virus, and oidyomycin.

Hyperglobulinemia, hypercalcemia, hemolytic anemia, neutropenia, thrombocytopenia and increased sedimentation rate and pulmonary insufficiency may occur.

Treatment of sarcoidosis is unsatisfactory. Vitamin D<sub>2</sub>, BCG vaccination, streptomycin, nitrogen mustard, urethane, tuberculin and anti-leprol have been used, but found to be of no value. Cortisone, 100 to 150 mg. daily in divided doses for a month to three months may be helpful. Upon termination of the therapy, relapses follow in the majority of cases.

Sodium intake should be restricted to 200 mg. a day for hospitalized patients and 500 mg. for ambulatory patients. A potassium supplement may be given in the form of the chlorides, 3 gm. daily. In the cases of ocular lesions it is imperative that the drug be used. In uveitis, particularly if the anterior segments are involved, drops of cortisone may be instilled directly into the eye or underneath the conjunctiva. However, if the posterior segments are involved, then ACTH intravenously, or cortisone orally in tablet form, is used. The effect of these treatments appears to be satisfactory.

As far as prognosis is concerned, many seem to recover spontaneously only to relapse later on. It has been estimated, however, that about 30 per cent recover permanently. This again is open to question. Some develop congestive heart failure resulting from cor pulmonale and about 25 per cent of them develop fatal pulmonary tuberculosis. In such a case there is always a doubt whether the condition was not tuberculosis from the beginning.

### SUMMARY

Sarcoidosis is a disease of unknown cause. The basic morbid anatomy regardless of the organ or tissue involved is the epithelioid cell tubercle without necrosis, having refractile or calcified inclusion bodies in the giant cells.

Lesions are usually widely disseminated. The tissues most frequently involved are lymph nodes, lung, liver, spleen, skin, eyes and bones, particularly of the hands. The heart, striated muscles, stomach, intestines, kidneys, bladder, pituitary and thyroid glands, and central nerves may also be involved.

The clinical course is usually chronic with minimal or no constitutional symptoms; however, there may be acute episodes of fever and malaise with or without signs or symptoms referable to the tissues and organs involved.

The intracutaneous tuberculin test is usually negative; the plasma globulins are often increased.

The outcome may be clinical recovery with radiographic evidence of residue, or impairment of function of organs involved, or a continued

chronic course of the disease. Treatment is unsatisfactory. Prognosis is uncertain.

### RESUMEN

La sarcoidosis, es una enfermedad de causa desconocida. La anatomía patológica básica sin tener en cuenta el órgano o tejido comprometidos, es el tubérculo de celdillas epitelioides sin necrosis, que contiene cuerpos de inclusión refractiles o calcificados en las celdillas gigantes. Las lesiones habitualmente están ampliamente diseminadas.

Los tejidos más frecuentemente afectados son los ganglios linfáticos, el pulmón, el hígado, el bazo, la piel, los ojos y los huesos especialmente, los de las manos. El corazón, los músculos estriados, estómago, intestinos, riñones, vejiga, la pituitaria, la tiroides y el sistema nervioso central, pueden también ser afectados.

La evolución clínica, es generalmente crónica con síntomas generales mínimos o ningunos; sin embargo, puede haber episodios agudos con fiebre, malestar con o sin síntomas referibles a los tejidos u órganos afectados.

La reacción intracutánea de tuberculina, es habitualmente negativa.

Las globulinas en el plasma, a menudo están aumentadas.

El resultado final, puede ser la recuperación clínica con evidencias de residuos radiográficamente o bien hay una evolución crónica de la enfermedad. El tratamiento no es satisfactorio. El pronóstico es incierto.

### RESUME

La sarcoïdose est une maladie de cause inconnue. Le substratum anatomique de la lésion, indépendamment du viscère ou du tissu atteint est le tubercle épithélioïde sans nécrose avec dans les cellules géantes, des inclusions de corps réfringents ou calcifiés. Les lésions sont habituellement largement disséminées. Les tissus le plus souvent atteints sont les ganglions, le poumon, le foie, la rate, la peau, les yeux et les os, en particulier ceux de la main. Le coeur, les muscles striés, l'estomac, les intestins, les reins, la vésicule biliaire, les ganglions hypophysaires, et thyroïdes ainsi que le système nerveux central peuvent être également atteints.

L'allure clinique est généralement chronique, ne s'accompagnant que de symptômes minimes ou peu caractéristiques. Toutefois, il peut y avoir des épisodes aigus, de la fièvre et des troubles généraux comportant ou non des symptômes dûs à l'atteinte de certains tissus ou de certains organes.

Habituellement, les réactions tuberculiques sont négatives. Souvent, il y a augmentation fréquente des globulines plasmatiques.

L'évolution peut se faire vers une guérison clinique s'accompagnant de séquelles radiographiques ou vers un trouble fonctionnel des organes atteints ou encore vers la chronicité de l'affection. Aucun traitement ne donne satisfaction. Le pronostic est incertain.

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# Unusual Lung Conditions Simulating Tuberculosis\*

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This is a paper from "Bella Vista" Sanatorium of Asunción, Paraguay, for tuberculous patients. In seven years, from 1945 to 1952, 1,246 patients have been discharged of whom 100 (8 per cent) were non-tuberculous. Some of these patients were sent as tuberculous, some others were admitted with diagnostic doubts for further study, but could simulate more or less tuberculosis.

## 100 PATIENTS WITH CONDITIONS SIMULATING TUBERCULOSIS

1) Inflammatory Diseases .....	35
Acute pneumonopathy .....	14
Fibrosis .....	4
Transient infiltration .....	3
Loeffler's syndrome .....	6
Abscess of the lung .....	7
Pneumoconiosis .....	1
2) Tumors .....	16
Primary cancer of the lung .....	8
Metastatic cancer .....	2
Metastatic pleural tumor .....	2
Cancer of the esophagus .....	1
Endothoracic goiter .....	1
Hamartoma of the lung .....	1
Indeterminate tumor .....	1
3) Broncho-Pulmonary Malformations .....	13
Pulmonary agenesis .....	1
Alveolar agenesis .....	6
Polycystic lung .....	2
Emphysema with giant bullae .....	4
4) Bronchial Diseases .....	13
Foreign body .....	1
Bronchiectasis produced by foreign bodies .....	2
Bronchiectasis .....	11
5) Pleural Diseases .....	7
Benign pneumothorax .....	2
Cholesterine pleurisy .....	2
Traumatic empyema .....	2
Traumatic pneumothorax .....	1
6) Foreign Bodies in the Lung .....	4
7) Without Pathologic Alterations .....	6
Without alterations .....	3
Positive sputum previous to admittance, but negative afterwards .....	3

8) Miscellaneous .....	6
Banti's disease .....	1
Purulent pericarditis .....	1
Acute endocarditis .....	1
Pulmonary infarct .....	1
Sarcoidosis ..	1
Indeterminate abdominal lymphangitis .....	1

### SUMMARY

One hundred cases of non-tuberculous conditions are reported. They were patients admitted to "Bella Vista" Sanatorium of Asunción, Paraguay, sent to us as tuberculous cases or for a better study. The 100 cases are divided in the following categories: 35 inflammatory diseases; 16 tumors; 13 malformations; 13 bronchial diseases; 7 pleural diseases; 4 foreign bodies; 6 without disease; 6 miscellaneous.

### RESUMEN

. Se relatan cien casos de afecciones no tuberculosas. Se trata de casos de enfermos ingresados al Sanatorio Bella Vista de Asunción, Paraguay, que nos han sido enviados para mejor estudio como afectados de tuberculosis. Los cien casos se agrupan como sigue: 35 de afecciones inflamatorias; 16 tumores; 13 malformaciones; 13 afecciones bronquiales; 7 afecciones pleurales; 4 cuerpos extraños; 6 sin enfermedad; 6 diversos.

### RESUME

Les auteurs rapportent 100 observations de malades non tuberculeux. Il s'agissait de malades hospitalisés au Sanatorium Bella Vista d'Asuncion (Paraguay) avec le diagnostic de tuberculose ou pour mise en observation. Les 100 cas se répartissent comme suit: 35 affections inflammatoires; 16 tumeurs; 13 malformations; 13 affections bronchiques; 7 affections pleurales; 4 corps étrangers; 6 sans aucune affection; 6 divers.

# Left Heart Failure in the Newborn

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The development of acute left heart failure in the newborn is rather an unusual event. It is apparent that only a few diseases can produce sufficient strain on the left ventricle to produce this particular syndrome. In the presence of left heart failure in the newborn, one should suspect coarctation of the aorta as a cause. It has been stated both by Blackford and by Abbott that coarctation of the aorta is of little clinical significance in infancy. They predicate this belief on the fact that in the two types of coarctation, the infantile type is fatal because of other associated severe anomalies of the heart, and the adult type has sufficient circulation to carry on the normal functions of the cardiovascular system. Aortic coarctation may be classified according to the relationship of the stricture in the aorta to the ductus arteriosum. A coarctation may have the stricture proximal to the aortic mouth of the ductus, or at the level of the ductus or distal to the ductus. Since the constriction exists before the birth of the child, it is obvious that the position of the ductus is very important in determining the degree and extent of the collateral circulation that develops. Evidence suggests that collateral circulation occurs whenever the demand for it is present. It is possible for such collaterals to be present before birth. In failure of development of adequate collateral circulation it becomes apparent that a strain may be placed on the left heart and left heart failure may appear. The two following cases of coarctation of the aorta in the newborn associated with acute heart failure are presented:

## *Chart No. D-81453, Autopsy No. A-51-6. Baby Girl R.*

The baby was born on the 2nd of February 1951, at 2:30 A.M. and died at 11:30 A.M. on the same day. At 8:30 A.M. on the day of birth, the child seemed to have a mild cyanosis and a strangling type of cry. Occasionally, the patient had a convulsion. The physical examination was negative. The abdomen was distended but no rectal obstruction was found. The child began to vomit bloody-green mucus and the reflexes became hyper-active. The platelet count at 5:30 A.M. was 170,000. The patient was given parathyroid, penicillin, and supportive measures. The blood sugar was 70 mgm. The child had more convulsions and then developed a paroxysmal dyspnea and finally the dyspnea became marked and was associated with cyanosis and ultimately rales were present in the chest. Bloody mucus escaped from both the nose and mouth terminally. The Wasserman test was negative. The hemoglobin was 94 per cent, the red count 4,800,000, the white count 32,600 and the differential count was normal. An x-ray film of the chest was unsatisfactory because of motion. The only finding of interest at necropsy was in the heart. There was a marked coarctation of the aorta. The aorta itself exhibited a curtain-like constricting ring extending transversely across the lumen approximately 1 cm. distal to the left subclavian artery. This

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constricted area of the aorta was opened and it was one-third of the width of the normal aorta indicating that the circumference of the aorta was not over at the most one-third of normal size. The ductus arteriosus was patent and was normal in appearance and in position. On microscopic examination nothing of note was found except for marked pulmonary edema.

*Chart No. B-AO 231, Autopsy No. A-5123.*

The patient was born six weeks before admission to the hospital on December 1, 1950 and death occurred on the 19th of December 1950 at 8:10 A.M. At three weeks of age, the parents noted the child had no desire to eat, had lost weight and was obviously dyspneic. The infant was large at birth and fed well while in the nursery, but on going home, the child began to fail in health. The child had difficulty in breathing. This dyspnea was evident on admission to the hospital. The dyspnea was mild at the start and then increased in severity. On physical examination, the child was very ill and rales could be heard in the left lung. The heart tones were normal and no masses could be found. The hemoglobin was 87 per cent, the red count 4,520,000, the white count 19,000, and the differential count was normal. The child was given oxygen. The x-ray examination revealed an enlargement of the heart. The urine revealed 2+ albumin, 4+ sugar with a trace of acetone. The white blood count on the day following admission was 27,400 and the hemoglobin was 103 per cent. The child developed a pneumonia which responded to treatment. On the 11th of December, rales appeared in both lung fields. On the 13th of December, the child had weakened and the dyspnea had increased and the child died on the 19th hospital day. The heart weighed 80 grams and showed marked hypertrophy of right and left ventricular walls. The enlargement on the right was more marked than that of the left. There were no abnormalities in the heart itself but the pulmonary artery was quite ectatic. The coronary circulation was normal. The root of the aorta was normal and opened into the pulmonary artery by a very wide ductus. The vessels that went to the neck were greatly dilated. There was a very marked constriction of the aorta just distal to the left subclavian artery representing a typical coarctation of the aorta. The pulmonary artery was dilated. The pancreas on close examination showed nothing remarkable but on microscopic examination, there was extensive interstitial fibrosis with dilatation of some of the ducts and these were filled with precipitated protein. The final diagnosis was coarctation of the aorta with patent ductus arteriosus and congestive heart failure as well as cystic fibrosis of the pancreas.

*Conclusions:* The recognition in infancy of coarctation of the aorta as a cause of left heart failure is imperative, for immediate surgery can cure the condition. This is a feasible operation and can be readily accomplished if one recognizes the inherent nature of the heart failure and the possibility that coarctation of the aorta is the underlying cause of the heart failure.

### SUMMARY

Two cases are reported in which left heart failure occurred in early infancy as a result of coarctation of the aorta. The salient clinical features are noted and the criteria for diagnosis is emphasized.

### RESUMEN

Se describen dos casos en los cuales se observa insuficiencia del corazón izquierdo en la primera infancia como resultado de la coartación de la

aorta. Las características clínicas más sobresalientes, serán detalladas y se hará mención especial de los criterios para el diagnóstico.

#### RESUME

On rendra compte de deux cas où un arrêt à la gauche du coeur s'est déclaré dans la première enfance comme résultat de la coarctation de l'aorte. Les principaux symptômes seront notés et les criteriums du diagnostic seront signalés.

# Hamartoma Simulating Ipsilateral Metastasis in a Case of Primary Bronchogenic Carcinoma

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Although primary carcinoma of the lung is fairly common, representing about 10 per cent of all carcinoma cases seen at autopsy,<sup>1</sup> the co-existence of a benign pulmonary hamartoma must be rare. Fortunately, in the case to be presented, the two lesions were in the same lung so that pneumonectomy removed both tumors. Had the benign lesion been in the contra-lateral lung, it would have been considered to be a metastasis from the bronchogenic carcinoma and the patient would have been denied the benefit of surgery.

## *Case Report*

D.K. Case 144698. A 71 year old white male was admitted to the Thoracic Surgical Service of the Hospital for Joint Disease on March 27, 1951 with a history of having had productive cough and fever three weeks prior to admission. At that time, physical examination revealed signs of pneumonia of the lower lobe of the left lung which was treated with penicillin. The symptoms disappeared but roentgen examination revealed a residual infiltration lesion of the left upper lobe which was suggestive of pulmonary neoplasm and hospital admission was recommended.

*Past History* was negative except for benign prostatic hypertrophy which was treated at another hospital two years previously by supra-pubic prostatectomy. Upon admission, he presented no weight loss, hemoptysis or expectoration.

*Physical Examination* revealed dullness to percussion of the left chest down to the level of the third thoracic spine with diminished breath sounds and vocal and tactile fremitus. No adenopathy was present. The remainder of the examination was negative.

*Laboratory* examinations of urine, blood, non-protein nitrogen, total protein, inorganic phosphatase, alkaline phosphatase, acid phosphatase and chlorides and hemogram were all within normal limits.

*Roentgenograms* of the chest taken April 4 (Figure 1) and laminograms on April 7, 1951 (Figure 2) showed a large globular area of infiltration extending from the hilum of the left lung into the apex at the level of the second intercostal space. In addition, a large fibrotic nodule or area of infiltration was noted in the plane of the fourth intercostal space. This was interpreted as probable bronchogenic carcinoma of the left upper lobe with adjacent pneumonitis and ipsilateral metastasis. Roentgenographic examination of the long bones was negative for metastases.

*Bronchoscopy* was performed on April 16, 1951 and revealed the trachea deflected to the right with visualization of the left upper lobe orifice not possible due to the anatomical arrangement. No infiltration, obstruction or neoplasm was noted within the range of bronchoscopic vision and no biopsy was taken. Papanicolaou smears from the left main bronchus showed no abnormal or atypical cells.

*Sputum Examination* by the Papanicolaou method, however, showed occasional clusters of deeply staining cells with hyperchromatic nuclei. These were considered as atypical cells but without malignant features.

*Operation* was performed on April 28, 1951 under endotracheal ether, cyclopropane anaesthesia in the "face-down" position. The sixth rib as well as a short posterior segment of the fifth were removed. The pleural space could not be

entered due to synechias between visceral and parietal pleurae so that an extra-pleural approach was used and a pleuro-pneumectomy performed. After the apex was brought down by blunt and sharp dissection, the mediastinum was found to be flaccid and uninvolved except for some large, soft, edematous lymph nodes which were removed with the lung. Individual cotton ligatures were used on vessels, and five silk plication sutures on the bronchus in the manner of Overholt.<sup>2</sup> The pleural cavity was thoroughly irrigated with saline and one tube dependent thoracostomy performed. Silk was used in layers for closure.

*Post-operative Course:* The drainage tube was removed after 24 hours. On the second post-operative day, he became slightly dyspneic and his skin was found to be cold and moist despite normal temperature and blood pressure. The pulse was grossly irregular and an electrocardiogram revealed many supraventricular premature contractions. He was digitalized with digoxin but maintained a tachypnea and fine moist rales at the right base for two weeks post-operatively (Figure 3). On May 30, 1951 he was discharged to a convalescent home where he remained for several weeks prior to returning home. He was seen at the Thoracic Surgical Clinic on October 18, 1951 where roentgenogram revealed obliteration of the left hemi-thorax by diffuse opacity without fluid level and only slight ipsilateral shift of the mediastinum; the right lung appeared normal. He had no complaints. There was no dyspnea on ordinary activity and the heart showed regular sinus rhythm. No lymph nodes were palpable.

*Specimen:* The lung was cut immediately after pneumonectomy, and unfortunately in doing so it was rendered unsuitable for photography. An irregular area of consolidation was present involving about two-thirds of the left upper lobe and extending into the apex. The upper lobe bronchus was patent for about 0.5 cm. and was occluded at this point by a friable whitish mass which infiltrated the bronchial wall. Upon pressure over the substance of the induration, a moderate amount of green, purulent material could be expressed. The indurated area extended almost to the visceral pleura at the periphery and contained numerous dilated bronchi and small saccular and cylindrical cavities which represented bronchiectasis and early abscess formation. The surrounding pulmonary parenchyma was atelectatic, firm and showed marked evidence of inflammatory exudate, which extended to the interlobar fissure and the pleura. In the area of the lingula and 0.5-0.7 cm. below the anterior visceral pleura was a round 1.3 by 1 by 1.2 cm. circumscribed nodule of whitish semi-gelatinous tissue which could be enucleated from the lung parenchyma with ease. The surrounding pulmonary parenchyma was not adherent and was smooth after the nodule was enucleated. The nodule itself presented a rather friable center surrounded by whorls of thickened whitish tissue. The central area was more gelatinous or mucoid than the peripheral portion.

*Microscopic examination* revealed a rather well differentiated epidermal carcinoma of the left upper lobe bronchus with atelectasis and acute and chronic inflammation of the peripheral lung parenchyma (Figure 4). The nodule was found to be composed of irregular strands and islands of cartilage interspersed with fat cells, fibroblasts, smooth muscle fibers and bronchial mucosa (Figure 5). This was considered to be a benign hamartoma.

### Discussion

Warren and Gates<sup>3</sup> found 6.8 per cent of 2,829 autopsies on patients with carcinoma disclosed multiple primary lesions. Cahan, Butler and Watson<sup>4</sup> reported 20 cases of multiple primary carcinomata, one being a triple primary—breast, sigmoid and lung. Hochberg, Grayzed, Berson and Rosenberg<sup>1</sup> reported a fascinating case in which a fibrosarcoma and carcinoma were present in one lung with a hamartoma in the other. In addition, there





FIGURE 1

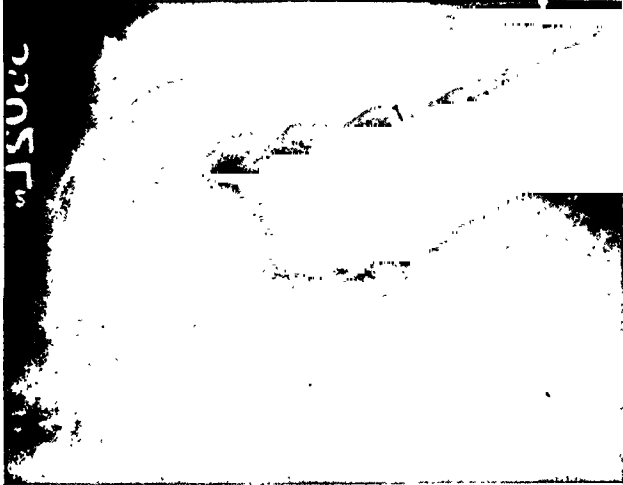


FIGURE 2



FIGURE 3

Figure 1: Pre-operative roentgenogram showing infiltrating lesion left upper lobe and solitary nodular density (Arrows).  
Figure 2: Pre-operative laminogram.—Figure 3: Roentgenogram on 12th post-operative day. Subsequent films show dis-  
appearance of fluid levels and subcutaneous emphysema.

were several benign tumors in six other organs. Unfortunately, no roentgenograms were published.

Albrecht in 1904 introduced the word "hamartoma" for a benign mixed tumor occurring in various organs including the lung. He considered these lesions not to be true tumors, but rather tumor-like structures composed of normal tissue of the organ arranged in an abnormal way or developed abnormally and showing varying degrees of differentiation of the individual tissues. The term "chondroma" still appears in articles<sup>5</sup> describing lesions such as these and should probably be discarded in favor of the more descriptive and accurate term "hamartoma." Bragg and Levine<sup>6</sup> found that about 100 pulmonary hamartomata have been reported mostly under the name of "chondroma". Of these, 75 per cent were discovered incidental to autopsy while the remainder were surgical findings. Less than 10 per cent, however, were correctly diagnosed pre-operatively.

It might be assumed that the tumor is a rare one from the small number of cases reported. That this is not so is confirmed by McDonald, Harrington and Clagett<sup>7</sup> who reported 23 cases from the Mayo clinic of which 20 were found incidentally at 7,982 necropsies and three were diagnosed correctly pre-operatively. This represents an incidence of 1 in 400 autopsies. Bragg and Levine<sup>6</sup> feel that the incidence of this tumor is greater than that of bronchial adenomata and is second only to bronchogenic carcinoma. Bronchial adenomata are more rapid in their growth, occur in larger bronchi and cause symptoms of obstruction and bleeding while hamartomata, on the other hand, are slow growing, usually sub-pleural and are not likely to produce symptoms leading to their discovery.

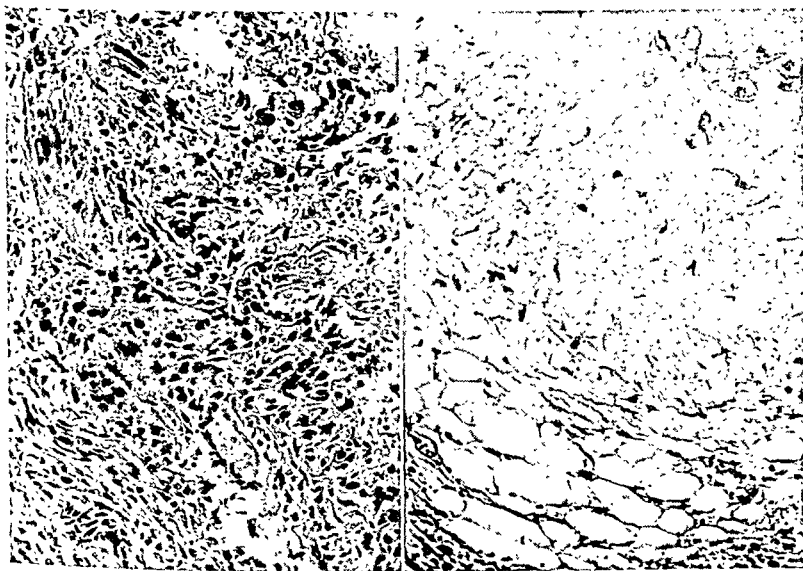


FIGURE 4

FIGURE 5

*Figure 4: Photomicrograph showing well differentiated epidermoid carcinoma of lung.—Figure 5: Photomicrograph showing benign hamartoma.*

Hamartomata are found three or four times as frequently in males as in females and have occurred in all ages from nine to 87 years. The distribution is roughly proportional to the relative size of the lobes, so that the lower lobe of the right lung is the most common location. They are most often solitary, the nodules ranging in size from a few mm. to 9 cm., the majority ranging from 0.5 to 3.0 cm. Simon and Ballon<sup>8</sup> report an 11 by 8 cm. hamartoma with obstructive symptoms causing pneumonia, bronchiectasis, brain abscess and meningitis which was erroneously considered to be a bronchogenic carcinoma. Though these tumors are practically always solitary, Ewing<sup>9</sup> quotes Virchow as describing multiple chondromata of the lung located at the root, in the parenchyma and on the pleura.

The gross appearance is characteristic. They are lobulated, round or spherical, sharply delineated from surrounding lung tissue and usually bound by a discrete capsule which strips easily. The cut surface is avascular, whitish, never anthracotic, with the consistency and appearance of layers of cartilage separated from other tissues. Areas of calcification or islands of bone formation may offer resistance to cutting.

The microscopic picture is also characteristic. The most prevalent tissue is cartilage arranged in irregular islands, sheets or strands or less commonly as a solid mass of cartilage. The irregular islands of cartilage are usually separated by areas of connective tissue, some of which are in various stages of mucoid degeneration and have an appearance not unlike mesenchymal tissue. Interspersed throughout, there may be epithelial or glandular tissue elements resembling that of small bronchi lined by simple cuboidal or columnar cells which may be ciliated. These glands occasionally produce mucous pockets. Fibrous tissue, smooth muscle and bone are occasionally present and it is not unusual to find scattered groups of mature fat cells, especially at the periphery (Figure 4).

Diagnosis by roentgenogram is not always possible but should be made more often than it has been in the past. The appearance of a solitary sharply demarcated round or spherical tissue with lobulated margin surrounded by normal lung tissue usually located peripherally or sub-pleurally and occasionally showing patchy areas of calcification on tomogram with areas of lesser density or fuzziness at the periphery should be suggestive of a hamartoma.

Since malignant change in a hamartoma is rare, the importance lies in differentiating this from other dangerous lesions. Of these, bronchogenic carcinoma is most important to rule out. The latter are faster growing and if calcification is present, bronchogenic carcinoma is unlikely. A solitary pulmonary metastasis may be impossible to differentiate from hamartoma without calcification, as in the case presented. Since solitary metastatic lesions are now resected in selected cases,<sup>10,11</sup> thoracotomy and frozen section may decide between simple enucleation and radical lobectomy or pneumonectomy. Bronchial adenoma may occasionally resemble hamartoma, but symptoms of bleeding, obstruction, hilar location and bronchoscopy should ensure diagnosis. Pulmonary "tuberculomata" may be indistinguishable from hamartomata, especially since areas of calcification may

be seen in both. When a history of tuberculosis is not obtainable, the presence of a peri-tuberculomatous inflammatory reaction may present a fuzziness or haziness so that they may occasionally be indistinguishable from hamartomata. As more tuberculomata are resected many additional hamartomata will be discovered.

#### ADDENDUM

The patient expired on August 24, 1952. Autopsy revealed metastases to tracheal lymph nodes and liver with invasion of right diaphragm. Bronchial stump showed no carcinoma. An incidental finding was a thyroid adenoma.

#### SUMMARY

A case is reported of primary bronchogenic carcinoma with co-existing hamartoma of the same lung in a 71 year old male. Pre-operatively, the benign lesion was thought to be an ipsilateral metastasis and pneumonectomy was successfully performed. Fortunately, the two tumors were in the same lung. Otherwise, the lesions would have been considered inoperable. The possibility of multiplicity of tumors, benign or malignant, has been stressed.

#### RESUMEN

Se refiere un caso de carcinoma bronquiogénico primario con hamartoma coexistente en el mismo lado pulmonar en un hombre de 71 años. Antes de la operación la lesión benigna se creyó que era una metástasis ipsilateral y la neumonectomía fué realizada con éxito. Afortunadamente los dos tumores estaban en el mismo pulmón pues de otra manera se hubiera considerado un caso inoperable. Se reclama la posibilidad de la existencia de tumores múltiples benignos o malignos.

#### RESUME

Les auteurs rapportent l'observation d'un homme de 71 ans, atteint d'un cancer primitif des bronches associé à un hamartome du même poumon. Avant l'intervention, la tumeur bénigne fut considérée comme une métastase et l'on pratiqua avec succès une pneumonectomie. Il est heureux que les deux tumeurs se trouvaient dans le même poumon. Dans l'autre cas, les lésions auraient été considérées comme inopérables. Les auteurs insistent sur la coexistence possible de tumeurs multiples, les unes bénignes, les autres malignes.

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# Massive Pulmonary Hemorrhage Due to Sarcoidosis

## Report of Two Cases\*

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Sarcoidosis continues to be a perplexing disease, the etiology of and the treatment for which remain obscure. No longer is the name "benign lympho-granulomatosis" applicable, for it is now known that sarcoidosis is capable of producing irreversible destructive changes and may per se be responsible for death. Since this disease may affect any organ of the body, it is understandable that symptoms and signs referable to the organ involved can and do simulate those of other more common disease-states involving these organs. Although pulmonary involvement due to sarcoid is common, certain forms are distinctly unusual and the diagnosis under such circumstances can be elusive. The clinical background and the character of the pulmonary lesions in the two cases presented were so confusing that reporting them seemed to be warranted.

*Case 1:* L.M. (or L.A.), a colored woman, age 33, was first seen at the Jefferson Hospital during October 1948. At that time she was found to have extensive pulmonary disease with left pneumothorax (Figure 1). Although she recalled having had no pulmonary complications following illnesses in childhood, she was certain that clubbing of the fingers had been prominent since approximately the age of 15. Approximately four years previously she had migratory arthritis and recurrent tender "spots" on her skin which subsequently left depigmented areas. This condition was repeatedly referred to by internists and dermatologists as vitiligo. There had been no known exposure to tuberculosis, she had not traveled in the coccidioides belt and there was no history of occupational exposure. For years she had been employed as a cook in a small restaurant.

In February 1950, when she consulted a chest specialist because of increasing cough and shortness of breath, numerous sputum examinations for tubercle bacilli and tuberculin skin tests were negative. She was told that the x-ray examination of the chest demonstrated extensive cystic changes and that she had cystic disease of the lung. By April 1950 (Figure 2) cough and dyspnea were ingravescent. She was so short of breath that she had to sleep in the erect position and she could not speak a full sentence without having to stop to catch her breath. Coughing spells were worse in the morning upon first getting up and upon lying down in the evening. She estimated that she raised approximately a cupful of purulent sputum daily and had observed blood-streaking at times. During the past year she lost approximately 20 pounds. There had been non-seasonal wheezing, worse at night, and intermittent attacks of watery nasal discharge. In spite of all of these difficulties she had continued to work regularly.

In May 1950, the temperature was normal, the pulse rate was 124, respirations were 34, the blood pressure was 90/70 and her weight was 100½ pounds. She was a tall, slender, well developed but poorly nourished Negress. Pallor of the mucous membranes, clubbing of fingers and toes and patchy distribution of vitiliginous lesions, localized for the most part over the arms and the upper half of the torso, were immediately obvious. No peripheral adenopathy was observed. The chest was long and thin with gross deficiency of subcutaneous tissue. Respiratory excursions

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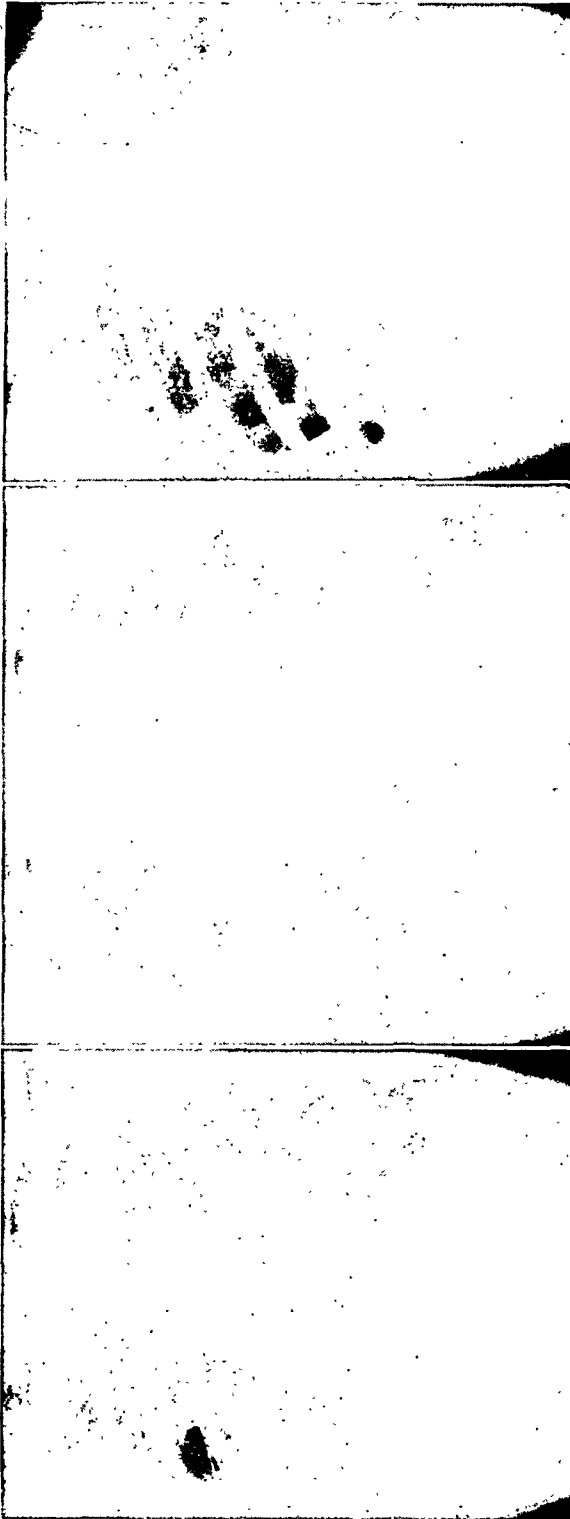


FIGURE 1

FIGURE 2

FIGURE 3

*Figure 1:* Demonstrates extensive bilateral bullous emphysema, patchy pneumonic infiltration, bilateral pleural reaction, broadened right upper mediastinal shadow and spontaneous left apical pneumothorax.—*Figure 2:* Shows disappearance of pneumothorax, variations in emphysematous blebs and pneumonic densities. The right upper mediastinal shadow is still prominent.—*Figure 3:* Great variation in size, shape and extent of emphysematous bullae and pneumonic densities. There is now obvious cardiac enlargement. The tremendous increase in bleb formation is obvious.

were limited and there was dullness over the right side posteriorly. There was great variation in the character of breath sounds—over some areas classical emphysematous breathing was heard; elsewhere breath sounds were entirely absent. Constant moisture was heard over both lower lung fields but without wheezes. The only discernible abnormalities on examination of the heart were the rapid rate and a significant increase in the intensity of the second pulmonic sound. The liver and spleen were not palpably enlarged and there was no edema.

Basic laboratory data disclosed normochromic anemia, leucocyte count of 9,300 cells/cmm. and differential count well within normal limits save for 9 per cent eosinophils. The urine was negative. Numerous sputum studies were negative for acid-fast organisms but a direct study of the sputum was reported as being loaded with monilia. The blood Kahn test was negative.

Over a period of several weeks she was given large doses of iodides and an anti-histamine with subjective and objective improvement in cough, expectoration, shortness of breath and vasomotor rhinitis. During July 1950 increased pulmonary bleeding occurred at the time of her menstrual period. Two days prior to the onset of the next menstrual period there began significant pulmonary bleeding which ceased spontaneously with the cessation of menstruation. Subsequent to that time she had large pulmonary hemorrhages on several occasions not associated with menstruation. She was lost sight of until February 1951 when she came to the Hillman Hospital Clinic because of abnormal vaginal bleeding of two months duration. Menstrual periods had ceased several months previously followed by some spotting. A clinical diagnosis of cancer of the cervix was confirmed by tissue study and she was given a course of x-ray therapy followed by radium.

On July 7, 1951, she was admitted to the Hillman Hospital because of profuse pulmonary bleeding. Sputum studies again disclosed monilia in profusion. On two occasions a rare acid-fast organism was suspected on concentrated material but three cultures of the sputum for tuberculosis and tuberculin skin tests remained negative. The admission hemogram was as follows: hemoglobin 9.7 gm. (63 per cent), red blood cells 4.36 million, leukocytes 5,700 with a differential count of mature polymorphonuclears—68, stab forms—5, lymphocytes—17, monocytes—1, eosinophils—5, basophils—4 per cent. The corrected sedimentation rate (Wintrobe) was 43 mm./hr. The urine showed one plus albumin and 5-6 wbc./hpf. Total proteins were 7.6 gm. per cent with 2.7 albumin, 4.9 globulin and a ratio of 1:1.8. The blood urea nitrogen was 19 mg. per cent. Biopsy of a vitiliginous lesion was interpreted as being consistent with sarcoidosis. X-ray films of the hands and feet showed "cystic and lace-like trabeculations in the phalanges consistent with the diagnosis of Boeck's sarcoid." She was discharged on July 25.

Again she was lost sight of for a number of months but was admitted to the St. Vincent's Hospital in Birmingham on December 7, 1951, because of large pulmonary hemorrhages which continued briskly for two days after admission (Figure 3). Apparently she withheld information with reference to her previous hospitalizations. Laboratory data disclosed a profound anemia but no tubercle bacilli. Bronchoscopy revealed rotation of the bifurcation to the left, and a bloody discharge from the right upper and lower lobes. No tumor cells were found. She was discharged on December 27, 1951, and went to another city where she died several days later. Necropsy was not obtained.

Comment: There are several points of interest in addition to the character of the pulmonary lesion and the gross pulmonary hemorrhages. There is a long-standing history of digital clubbing which obviously was present years before the onset of pulmonary symptoms. Pneumothorax has been reported in sporadic cases of sarcoidosis. It is of interest that the vitiliginous lesions still showed changes consistent with sarcoidosis. This experience indicates the wisdom of obtaining biopsies of presumably simple skin lesions



in the presence of undiagnosed disease of the chest. The presence of monilia in the sputum among individuals with chronic pulmonary disease is generally regarded as a common contaminant. However, contributors from Scandinavia ascribe some significance to this finding among sarcoidosis patients. (On speculative grounds, one might question the wisdom of using broad-spectrum antibiotics in patients demonstrating this degree of superimposed moniliasis). The observation of questionable vicarious menstruation and the subsequent development of cancer of the cervix are undoubtedly coincidental.

*Case 2:* A.L., a colored female, age 52, was admitted to the Lloyd Noland Hospital in Fairfield, Alabama, on January 27, 1952, because of shortness of breath. Apparently she had been well until approximately six weeks previously when she observed mild bilateral flank pain which radiated into both breasts. For approximately one week prior to admission she had fever ranging from 101 to 102 degrees F. daily. Shortness of breath became so severe that she required four pillows at night. She was seen in the clinic 10 days before admission with slight fever, tachycardia of 120 and respirations of 32 per minute. Examination of the chest disclosed a friction sound over the left lower lobe, moist rales and gross suppression of breath sounds over this area. An x-ray film of the chest at that time was interpreted as being consistent with cardiac decompensation (Figure 4). After three days of penicillin therapy, the temperature became normal, the pulse rate dropped to 88, but respirations remained 32 per minute. There was considerable improvement in her ability to breathe comfortably but four days later respiratory difficulty returned. When seen in the clinic at this time, respirations were 40 per minute, the friction sound had disappeared, rales and breath sound changes persisted, but it was now observed that the second pulmonic sound had become tympanic.

There was some doubt as to whether an illness at age 10 had been correctly diagnosed as having been smallpox. She denied having had any illness whatsoever during the past five years. The family history, occupational history, history of

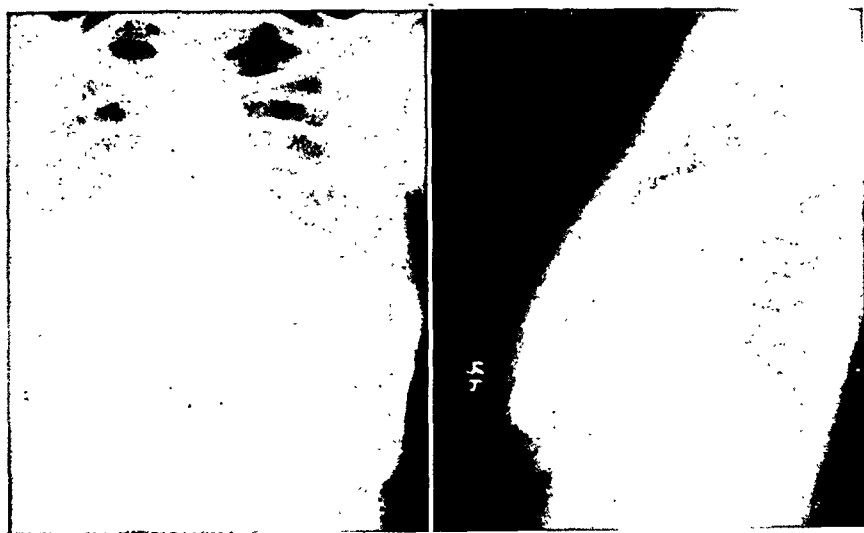


FIGURE 4: Demonstrates large bleb right apex, reticulated and nodular changes both lung fields, a triangular cardiovascular shadow and dense pneumonic infiltration in the right lower lung field. The right lateral film demonstrates that the pneumonic infiltration is almost completely confined to the limits of the right middle lobe.

exposure to tuberculosis and a review of systems disclosed no contributory information. She had noted no shortness of breath prior to the onset of the present illness.

The oral temperature was 99, the pulse rate varied from 96 to 112 and respirations were 32 per minute. The blood pressure was 108/70 and her weight was 127¼ pounds (significantly below her usual weight). She was a well developed but slightly undernourished patient lying flat on her back but obviously tachypneic. Sticky moist rales were found over both lower lung fields and in the axillae. The heart was thought to be enlarged and somewhat triangular in contour. The second pulmonic sound was tympanitic and greater than the second aortic sound. Although no murmurs were observed, an inconsistent pericardial friction sound was heard. The liver and spleen were not palpably enlarged, no significant glandular enlargement was detected and there was no edema.

Laboratory data disclosed no evidence of anemia; the leukocyte count and differential were normal with 5 per cent eosinophils; the urine was negative; the blood Kahn test was negative; the sedimentation rate was 27 mm./hour (Cutler); the blood urea nitrogen was 25 mg. per cent; a sickle cell preparation was negative; the venous pressure and circulation time were normal; the vital capacity was 1.2 liters (38 per cent); a 1:10,000 Mantoux test was negative and numerous sputum specimens for acid-fast bacilli were negative. An electrocardiogram made two days after admission was interpreted as follows: "Rate 125. Low voltage. Small Q1. Inverted T waves in limb lead and in V2, V4 and V6. Consistent with myocardial disease and suggests pericardial effusion."

During the hospital stay it was found that digitalization and mercurial diuretics were of no benefit. On the day before discharge an intermittent gallop was detected in the pulmonic area and an apical pericardial friction sound was heard by several observers. She was discharged on February 1, 1952, with the diagnosis of acute benign non-specific pericarditis with pulmonary parenchymal involvement. While under observation in the clinic she gained weight gradually. Tubular breath sounds became apparent over the right middle lobe. She was presented at Staff Conference on March 5, 1952, at which time the diagnosis of sarcoidosis was first seriously entertained because of our experience with Case 1. Further laboratory studies were carried out. A 1:1000 Mantoux test was negative, total proteins were 8.0 gm. per cent with serum albumin of 2.96, serum globulin of 5.04 and a rate of 1:1.7. From April 15th until June 20, 1952, she complained of cough productive of green sputum and some vague chest pain. Although she had consistently run a low grade fever there had been a 10 pound increase in her weight.

On June 20, 1952, she began having blood-streaked sputum which was followed by a large hemorrhage. She estimated that she lost a "quart of blood". She was readmitted to the Lloyd Noland Hospital the following day. On examination, the temperature was normal, the pulse rate was 80, respirations were 24 and the blood pressure was 120/80. No abnormality of the heart was detected. Coarse rales with a "to and fro cracking sound" were heard over the right middle lobe region and occasional moist rales were heard over both lower lung fields. The liver edge was palpated two fingerbreaths below the right costal margin. The spleen was not felt and there was no detectable adenopathy.

Laboratory studies disclosed sedimentation rate of 21 mm./hour (Cutler); numerous sputa for acid-fast bacilli on this admission were negative; the total proteins were 8.8 gm. per cent with albumin of 3.0, globulin of 5.8 and a ratio of 1:1.9.

On June 22nd, she had a series of massive pulmonary hemorrhages rapidly filling three large emesis basins. The bleeding continued for more than an hour during which time she lapsed into shock. A liter of blood was given intravenously, following which shock was controlled and no further bleeding occurred. She was discharged several days later to the surgical service of the Jefferson Hillman Hos-

pital for a supraclavicular tissue biopsy.<sup>1</sup> During the course of this procedure a node was found which was described pathologically as being consistent with sarcoid.

### *Discussion*

These two cases appear to be of unusual interest because large pulmonary hemorrhages have rarely been observed among patients with proved sarcoidosis.

Riley reviewed 52 cases in the Bellevue Hospital series. There is reference to blood-streaked sputum in several instances, but no large pulmonary hemorrhage was observed.<sup>2</sup> Oblath and Farber studied 40 patients among whom four had small hemoptyses.<sup>3</sup> McCort et al., reported 28 cases of sarcoidosis among whom two had slight hemorrhages.<sup>4</sup> In all the reports where bleeding has occurred there has been no correlation with the type of pulmonary involvement as seen radiographically.

The only proved case of sarcoidosis with fatal pulmonary bleeding recorded in the literature is that of Fisch and Freireich.<sup>5</sup> Definite bronchial dilatation was found in this case. Israel has a case with fatal pulmonary bleeding who on necropsy was found to have emphysematous and bronchiectatic changes.<sup>6</sup> Freiman is of the opinion that large pulmonary bleeding among sarcoidosis patients is due to bronchiectatic changes.<sup>7</sup>

It is of passing interest that among 1,316 cases of pulmonary hemorrhage in one series, not one case was diagnosed as sarcoidosis.<sup>8</sup> Among 200 cases of hemoptysis reported from the Mayo Clinic only one was proved to have sarcoidosis, but there is no reference to the amount of bleeding or the character of x-ray findings.<sup>9,10</sup>

It would, therefore, appear that pulmonary bleeding of the magnitude observed in these two cases is, indeed, an unusual happening among patients with sarcoidosis. However, these patients exhibited pulmonary changes of the more unusual character seen in this disease. Perhaps more of these cases with large pulmonary hemorrhages due to sarcoidosis will come to light as clinicians become more generally aware that sarcoidosis is capable of producing fibrotic, bronchiectatic and emphysematous changes.

### SUMMARY

Two cases of large pulmonary bleeding due to sarcoidosis are added to the literature. The occurrence of unusual pulmonary lesions in sarcoidosis and the relationship to hemoptysis are stressed.

### RESUMEN

Se gragan a la literatura dos casos de gran hemorragia pulmonar debida a sarcoidosis. Se recalcan la ocurrencia de lesiones primarias pulmonares inusitadas y su relación con la hemoptisis.

### RESUME

L'auteur rapporte deux observations de grosse hémorragie pulmonaire due à la maladié de Besnier-Boeck-Schaumann. Il insiste sur la survenue

de lésions pulmonaires inhabituelles dans cette affection et leur relation avec les hémoptysies.

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# Cortisone Treatment of Sarcoidosis

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Until the introduction of cortisone, management of sarcoidosis was limited to supportive measures and was notoriously ineffective in controlling the incapacitating ocular and pulmonary lesions. In the past, Fowler's solution, x-ray, urethane, nitrogen mustard, calciferol and antibiotics have been found to be of no value in the treatment of this disease.

In 1950, Thorn et al. reported one case treated with ACTH with no response.<sup>1</sup> Sones and co-workers,<sup>2</sup> however, obtained marked improvement in two cases treated with cortisone. Their studies caused them to postulate that a relative adrenal insufficiency may be present in sarcoidosis, thus theorizing the better response to cortisone. At the time of writing, approximately 20 cases<sup>2-5</sup> of sarcoidosis treated with cortisone, with variable response, have appeared in the literature. We present the following case report as an addition to the literature:

This is a 25 year old negro airman admitted to the Wright-Patterson Air Force Base Hospital on June 19, 1952. He dated the onset of his present illness to sometime in January 1952, when he noted an insidious onset of small, indurated lesions of the skin about the ankles. He was ultimately hospitalized at Selfridge Air Force Base in May 1952, when there was a marked increase in the number of nodules with bilateral involvement of the lower legs. Also during this interval (from January to May) he noted photophobia, burning and lacrimation of the eyes with no associated visual disturbances. He observed easy fatigability, some loss of appetite, and a weight loss of approximately 15 pounds. He remarked that approximately two months prior to admission he noted for the first time some blood streaked sputum lasting for about two or three days. There was no recur-

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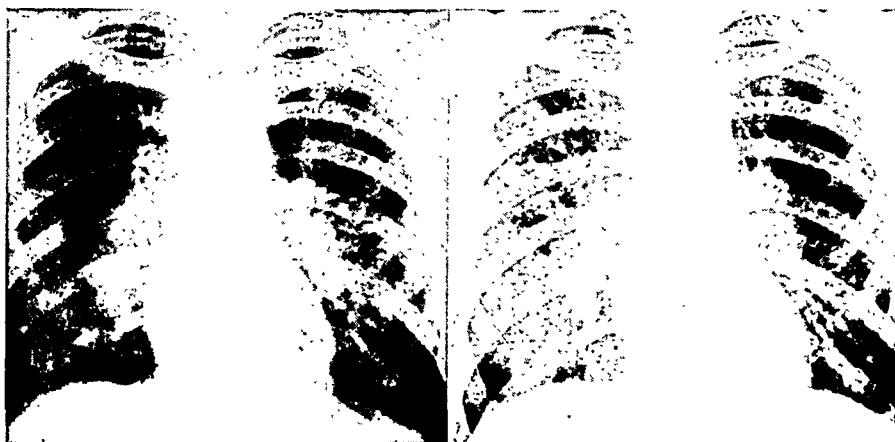


FIGURE 1

FIGURE 2

*Figure 1: Before Cortisone Therapy.*

*Figure 2: Two weeks after Cortisone Therapy.*

rence of this isolated incident. There has been some soreness of the anterior chest and subternally, made worse by movement. Skin biopsy from the right calf showed findings compatible with sarcoidosis. A chest x-ray film revealed bilateral enlargement of the hilar nodes with diffuse nodular infiltration throughout both lung fields. He was then transferred to this center for further evaluation and treatment.

*Past History:* Gonococcal urethritis in 1949 treated with penicillin; otherwise negative.

*Family History:* Also negative.

*Physical Examination:* At the time of admission to this hospital, the physical examination revealed a well-developed, well-nourished, colored male who appeared to be neither acutely nor chronically ill. Height 74 inches. Weight 184 pounds. Blood pressure 110/70. Pulse 80. Temperature 98.6 degrees F. No cervical lymphadenopathy. Chest was symmetrical with no limitation of motion. There was a decrease in the intensity of breath sounds uniformly over both lung fields. No other abnormalities were noted on auscultation or by percussion. Liver and spleen were not palpable. The skin of the thighs and legs were studded with multiple, solitary, indurated, non-tender reddish-brown nodules, too numerous to count (Figure 6). There was no palpable lymphadenopathy.

*Laboratory Data:* On admission to this hospital the hemoglobin was 15.1 grams per cent with 6,100 white cells—54 per cent of which were neutrophils, 34 per cent lymphocytes, 9 per cent monocytes, and 2 per cent eosinophils. Total protein 7.9 grams per cent with 5.3 grams per cent of albumin and 2.6 grams per cent of globulin. Blood calcium 10.2 mgms. per cent. Inorganic phosphorus 4.9 mgms. per cent. Acid phosphatase 1.1 units. Alkaline phosphatase 1.5 units. Repeat urinalyses were within normal limits. Sputum studies were negative for acid-fast bacilli and fungi. PPD first and second strength skin tests were negative. Histoplasmin: 4 plus. Coccidioidin: Negative. BSP showed no retention of dye in 45 minutes. Cephalin flocculation: 3 plus. Icteric index: 12.6. Thymol turbidity: 12 units. Cholesterol: 197 mgms per cent. Van den bergh, direct: Negative. Chest x-ray film (Figure 1) revealed evidence of fine nodular fibrosis throughout both lung fields. Multiple densities were present, together with bilateral enlargement of the hilar lymph nodes. Repeated corrected sedimentation rates during the course of hospitalization ranged from 35 mm./hr. to normal limits. Hemoglobin remained normal throughout hospitalization. Repeat serum protein on July 3, was 5.2 grams per cent of albumin, and 3 grams per cent of globulin. Repeat on

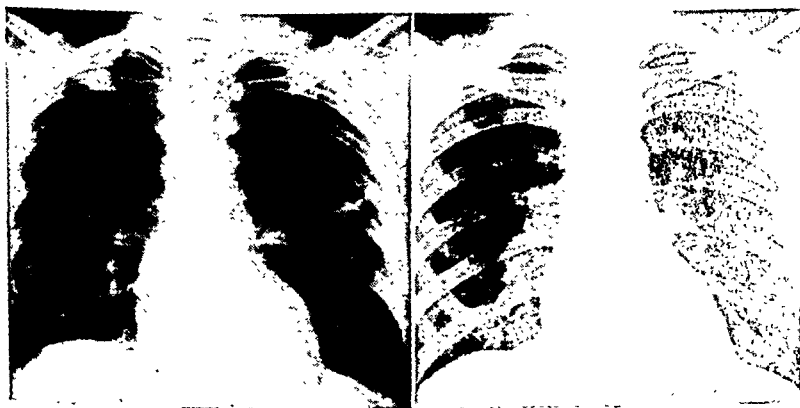


FIGURE 3

FIGURE 4

Figures 3 and 4: After Cortisone Therapy. Maximum clearance in Figure 3. Note increase in parenchymal lesions in Figure 4 (eight weeks after stopping Cortisone).



FIGURE 7: After Cortisone Therapy.

FIGURE 6: Before Cortisone Therapy.

November 10 showed 5.1 grams per cent of albumin and 3 grams per cent of globulin. Calcium was 11.3 mgms. per cent. Inorganic phosphorus 3.3 mgms. per cent. BUN 3.5 mgms. per cent. Maximum breathing capacity done in July on admission was 98.5 liters per minute.

*Course During Hospitalization:* Shortly after admission the patient was seen in consultation by the Eye Clinic because of complaints of slight burning, itching and photophobia. The consultant reported several small mutton-fat type "KP" areas on the endothelial surface of the corneas bilaterally. Except for small lace-like vitreous opacities, the vitreous was clear. It was his impression that the patient had uveitis, anterior, bilateral, granulomatous in type and compatible with the diagnosis of sarcoidosis. A biopsy of a skin nodule was done on July 11 and reported as compatible with sarcoidosis (Figure 5). During the course of pre-treatment observation, there was no evidence of fever or toxicity nor was any regression of the skin or lung lesions evident.

On August 7 he was started on cortisone receiving an average of 200 mg. daily. Within two weeks, the lesions on the legs began to fade and by September 11 they had completely disappeared (Figure 7). Also, at this time, the uveitis had completely resolved. Chest x-ray film of August 22 (after two weeks of cortisone) disclosed considerable parenchymal and hilar improvement (Figure 2). Cortisone was discontinued on September 11, 1952 after a total of 6 grams. Maximum improvement of the lung lesions was observed on the x-ray film of October 28 (Figure 3) though complete clearing did not occur. At the end of the period of treatment he had no complaints, felt very well, and had gained eight to 10 pounds.



FIGURE 5: Section of skin taken to show a non-caseating epithelioid granuloma characteristic of other lesions in the subcutaneous tissue. A Langhans type "giant cell" is to be seen in the lower portion of the field (and another at 2 o'clock). Compatible with sarcoidosis.



Maximum breathing capacity determined in November was 109.2 liters per minute as compared with the base line of 98.5 liters per minute. A repeat chest x-ray film in November, eight weeks after cortisone therapy had been stopped (Figure 4), showed a slight increase in the diffuse nodular infiltration of both lung fields as well as persistence of bilateral hilar lymphadenopathy. No eye or skin recurrences have appeared to date. Comparison of original and repeated electrolyte studies revealed no changes secondary to cortisone therapy.

### SUMMARY

A case of sarcoidosis with involvement of the eyes, the skin and lungs, treated with cortisone, is presented. Complete resolution of the uveitis and skin nodules occurred. The chest x-ray film revealed marked parenchymal and moderate hilar lymphadenopathy resolution, though complete clearing never was achieved. Eight weeks after completion of steroid therapy, an increase of parenchymal lesions was noted. These results compare with similar recent reports in the literature.

### RESUMEN

Se presenta un caso de sarcoidosis con compromiso de los ojos, la piel, y los pulmones, habiéndose tratado con cortisona. Se obtuvo la completa resolución de la uveítis y de los nódulos cutáneos. La película a los rayos X mostró resolución marcada del parénquima y moderada resolución de la linfadenopatía hiliar, aunque completo aclaramiento nunca se logró. Ocho semanas después de terminado el tratamiento con esteroides, se notó un aumento de las lesiones parenquimatosas. Los resultados son comparables a los similares referidos en la literatura.

### RESUME

Les auteurs rapportent un cas de maladie de Besnier-Boeck-Schaumann, avec atteinte des yeux, des téguments, des poumons, qui a été traitée par la cortisone. Il y eut une disparition complète de l'uvéïte, et des nodules cutanés. La radiographie montre une amélioration importante de l'atteinte parenchymateuse, et une action plus discrète sur les adénopathies hilaires. Toutefois, il n'y eut jamais un nettoyage complet.

Huit semaines après que le traitement ait été complété par l'action des stéroïdes, on constata un accroissement des lésions parenchymateuses. Les auteurs comparent ces résultats avec les observations récemment rapportées dans la littérature.

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# Pneumomediastinum in the Newborn:

## A Report of Three Cases

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In the past few decades, a great deal has been learned concerning the newborn who is dyspneic and in respiratory and circulatory distress. Great emphasis has been placed on trauma to the head occurring during parturition. Clogging of the respiratory passages and resultant atelectasis is a well known cause. Aspiration of amniotic fluid with formation of an amniotic membrane is occasionally found. Failure of the lungs to expand normally is a common factor in embarrassment of respiration and circulation. Certainly the majority of cases of respiratory and circulatory difficulty in the newborn are due to trauma or to atelectasis.

Occasionally congenital defects of the broncho-pulmonary system or the cardiovascular system will be at fault. There are reports of congenital cysts of the lung, congenital duplications of the esophagus, agenesis of a lung, tracheo-esophageal fistula, absence of the diaphragm or a portion thereof, and other unusual conditions leading to extreme distress in the newborn.

Recently, in three newborns, we have encountered respiratory and circulatory difficulty caused by pneumomediastinum and pneumothorax. All of these cases have improved spontaneously with conservative treatment.

*Case 1:* This infant was delivered at the St. Joseph Hospital on January 12, 1952. It apparently was normal at birth. The first stage of labor lasted eight hours, the second stage one hour, and the third stage 20 minutes. It was necessary to administer artificial respiration and oxygen under pressure to initiate breathing. Respirations were labored, the child was cyanotic, and breathed noisily. On the first day, it vomited some black material resembling blood. The following day, it was still necessary to continue oxygen because of the extreme cyanosis. On the third day of life, cyanosis was less and x-ray films disclosed mediastinal emphysema (Figures 1A and 1B). By the fourth day it was possible to discontinue the administration of nasal oxygen and respirations had returned to normal. On the fifth day, x-ray films disclosed almost no air in the anterior mediastinum (Figures 2A and 2B). It made an uneventful recovery and was dismissed on the eighth day of life, having regained its normal birth weight.

*Case 2:* This was a white female child born in St. Joseph Hospital in Fort Wayne, Indiana, on September 13, 1952, after an uneventful labor. The mother had had one previous normal child. Demerol had been administered sparingly during the labor, and drop ether was given the mother during the second stage of labor which lasted 18 minutes. The baby did not breathe spontaneously and was placed in an airlock. It was in the airlock for 12 hours and was given alpha lobeline, and caffeine sodium benzoate but remained listless and became cyanotic when removed from the airlock. At this time, physical examination revealed mediastinal crackles. A chest x-ray films disclosed air in the anterior mediastinum (Figures 3A and 3B). The child was closely observed and given nasal oxygen. It remained slightly cyanotic for two days but gradually the respirations became progressively less

grunting, the color improved, and at about this time left pneumothorax became evident (Figures 4A and 4B). Since the child was improving spontaneously, it was not necessary to tap the chest. Recovery was rapid and the child left the hospital on the seventh day of life, clinically well.

*Case 3:* This was a male infant weighing seven pounds and two ounces, born at the Fort Wayne Lutheran Hospital, January 20, 1953. About an hour and a half after delivery, the infant was noted to be cyanotic and respirations were rapid and grunting in character. Auscultation of the chest disclosed bronchial type respirations but no rales. He was placed in an oxygen tent with immediate improvement. The following day, a lateral x-ray of the chest disclosed air in the anterior medias-



FIGURE 1A



FIGURE 1B

*Figure 1A:* AP of chest at birth showing nothing remarkable.—*Figure 1B:* Lateral of chest showing the large amount of air in the anterior mediastinum.



FIGURE 2A



FIGURE 2B

*Figure 2A:* AP of chest disclosing a small left pneumothorax.—*Figure 2B:* Lateral of chest showing much less air in the anterior mediastinum.

tinum. Respirations were still rapid and grunting in character. Two days later, the baby appeared normal and did not require further therapy. He was dismissed on the sixth day of life.

#### *Historical:*

Pneumomediastinum, or airlock, was first called to attention by Guillot<sup>3</sup> in 1853. He presented two cases of mediastinal emphysema, discovered at post mortem examination. Since then, there have been occasional reports of its occurrence, and in 1940, DeCosta,<sup>1</sup> in a review of the world literature, found reports of 46 cases that had occurred in infants up to the age of 10 days. In 21 other reports, the children were over 10 days of age and in the early months of life. This latter group he attributed largely to congenital anomalies and inflammatory conditions.

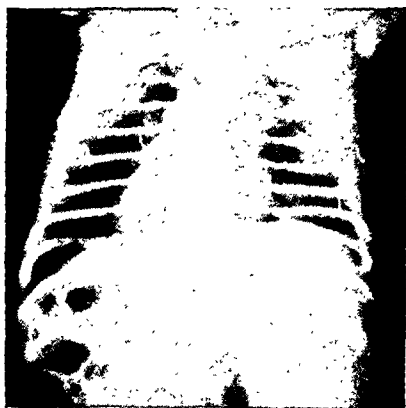


FIGURE 3A

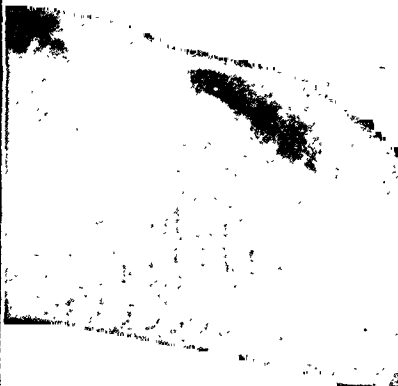


FIGURE 3B

*Figure 3A:* AP of chest showing nothing remarkable.—*Figure 3B:* Lateral of chest showing great quantity of air in the anterior mediastinum.

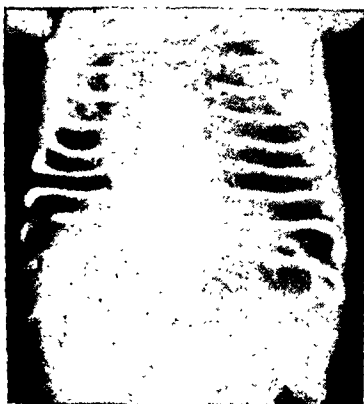


FIGURE 4A

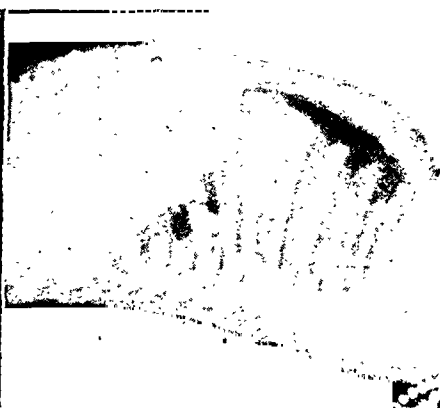


FIGURE 4B

*Figure 4A:* AP of chest showing a well developed pneumothorax and compression and crowding of the great vessels of the superior mediastinum to the right.—*Figure 4B:* Lateral of chest showing a decrease in the air in the anterior mediastinum.

*Etiology:*

Pneumomediastinum may be caused by a number of conditions.<sup>8</sup> Chest surgeons are quite familiar with post surgical and post traumatic pleural leaks with subcutaneous and mediastinal emphysema. Perforating wounds of the larynx, trachea, and bronchi may be accompanied by this condition. Perforating wounds of the diaphragm or the neck may admit air into the mediastinum. This thus may be a complication of head and neck surgery. Rupture of the esophagus is almost always complicated by mediastinitis with air. There have been a few cases following pneumoperitoneum.

When pneumomediastinum occurs in the newborn, it is most commonly due to congenital anomalies of the tracheo-bronchial tree or to excessive intra-alveolar pressure during attempts at resuscitation. Infection is generally not a factor in the newborn but in older children it may be a cause. Some cases apparently occur spontaneously and are never adequately explained. Such is illustrated by the third case.

*Pathology:*

Air is classically found in the anterior mediastinum and is best shown by lateral x-ray film. The studies of Macklin<sup>6</sup> and Fisher have been largely responsible for our understanding of the phenomenon. They showed that if alveoli are over-distended and alveolar rupture occurs, air can be forced along the extra-alveolar pulmonary vessels to the root of the lung. These vessels, being extrapleural structures, provide a direct pathway to the mediastinum. The air thus collects in the anterior mediastinum.

If the pressure in the anterior mediastinum is great enough, the air may rupture the mediastinal pleura and leak into the pleural cavity and produce pneumothorax. The other theory concerning the pathogenesis of pneumothorax is that it may come from a laceration of the surface of the lung. This is probably seldom the case for DeCosta<sup>1</sup> was unable to cause leakage through the visceral pleura with pressures of 100 millimeters of mercury whereas in the mediastinum, a pressure much less than this would regularly cause a rupture of the mediastinal pleura.

Should infection be conveyed from the ruptured alveoli, it would theoretically be possible for an inflammatory process of the lung to be initiated.

*Symptomatology:*

After considering the pathology of pneumomediastinum, the symptomatology is easily understood. The signs vary, depending on the degree of the process. Slight dyspnea may be the only sign, and it may easily pass for mild atelectasis. As the quantity of air becomes greater, marked interference with respiration may ensue. Cyanosis, rapid grunting respirations, and distention of the great veins of the neck will be evident. The presence of air in the mediastinum under pressure may be great enough to cause the above symptoms. In addition, air compressing numerous tiny pulmonary arterioles and venules may interfere with pulmonary circulation. If there is accompanying pneumothorax, additional interference with cardiopulmonary function may ensue. On the other hand, if there is a great degree

of mediastinal emphysema, and the mediastinal pleura ruptures with consequent pneumothorax, the symptoms may become milder because of release of the increased mediastinal pressure. If the air continues to be pumped from the alveoli into the mediastinum, symptoms will become worse unless prompt treatment is undertaken.

#### *Diagnosis:*

A high index of suspicion in all cases of respiratory and circulatory difficulty in the newborn is the first step toward a correct diagnosis. Frequently, a history of difficult resuscitation is obtained. It may not be present however, as is illustrated by case 3. A crackling sound in the mediastinum is almost diagnostic. In exceptional cases, air may be noted in the suprasternal notch. Real proof is forthcoming on lateral x-ray film inspection. Gumbiner and Cutler<sup>4</sup> have emphasized the value of chest x-ray films in illustrating this. Even though the anterior-posterior x-ray film fails to disclose an abnormality, one ought to resort to a lateral ray, for the air is more easily seen in the anterior mediastinum under such a view.

Apparently, pneumomediastinum is not so rare as one would be led to believe by the sparsity of reports in the literature. Davis and Stevens<sup>2</sup> found six cases of pneumothorax in the routine roentgenographic examination of 702 consecutive newborns. If pneumomediastinum precedes pneumothorax in such cases, the incidence of mediastinal emphysema of more than 1 per cent is probably a fact for not all cases of pneumomediastinum will produce pneumothorax.

#### *Treatment:*

Oxygen by mask or funnel is of great value in tiding the infant over the acute phase of circulatory and respiratory embarrassment. In many cases, symptoms are so mild that no treatment is necessary. If symptoms are increasing in severity, it is imperative to control the source of air. One should avoid applying positive pressure to the infant for fear of forcing more air into the mediastinum.

Should symptoms warrant, one must provide an outlet for the accumulated air. One may drain the anterior mediastinum through the third left intercostal space,<sup>4-7</sup> directing the needle medially until the air is reached and the tension released. If one is not able to release the air by means of a needle, a small incision at the suprasternal notch will provide an air outlet. If pneumothorax is marked, an intercostal catheter connected to negative suction, will provide for egress of air and allow the lung to expand.

A note of thanks is extended to Dt. Wallace Bash and to Dr. C. Wm. Goebel for permitting us to publish these cases.

#### SUMMARY

1) Three cases of mediastinal emphysema in the newborn have been presented.

2) A brief discussion of the etiology, historical background, symptomatology, pathology, diagnosis, and treatment has been given.

### RESUMEN

- 1) Se presentan tres casos de enfisema mediastinal en el recién nacido.
- 2) Se discuten brevemente la etiología, los antecedentes históricos, la sintomatología, la anatomía patológica, y el diagnóstico y tratamiento.

### RESUME

- 1) Les auteurs présentent trois cas d'emphysème médiastinal du nouveau-né.
- 2) Ils donnent une revue rapide de l'étiologie, l'historique, la symptomatologie, l'anatomie pathologique, le diagnostic et le traitement.

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# Broncholithiasis

## Report of a Case Occurring in Active Pulmonary Tuberculosis

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Standard medical texts omit the subject of broncholithiasis completely or merely acknowledge its existence. One must turn to the periodic literature to obtain detailed information. In view of the foregoing, it seems appropriate to briefly review the literature incident to reporting an additional case of broncholithiasis as occurring in the presence of active pulmonary tuberculosis.

*Incidence:* Although scattered references to broncholithiasis have appeared for hundreds of years, it is only since the latter part of the 19th century that the subject has attained any prominence, emphasis being most marked in the past decade. In 1941 Van Ordstrand<sup>9</sup> discovered 30 theretofore reported cases incident to reporting two additional cases. By 1946 Zahn<sup>10</sup> reporting on the one case of broncholithiasis discovered among more than 4,000 tuberculous patients stated that 71 cases had been reported prior to that time. In 1948 Freedman and Billings<sup>2</sup> added seven cases to the 96 reported in the literature. Schmidt et al.<sup>7</sup> in 1949 presented a masterful paper in which were reported 13 new cases. Since that time the Anglo-American literature, in articles and discussions thereof, has contained references which increase the number of cases of broncholithiasis reported therein to 142.<sup>3-5,11</sup>

*Etiology:* One may broadly classify broncholiths into two groups in accordance with their site of origin.

(a) Extrinsic calculi are those arising from aspirated foreign bodies including tissues, secretions and dusts and are formed within the bronchial lumen—a rare occurrence.

(b) Intrinsic calculi take their origin within the tissues proper of the lung, bronchi and lymph nodes and may be subdivided as follows:

(1) Senile calcifications of the elastic cartilage of the bronchi is a function of aging. Sequestration results in bronchial calculi.

(2) Metastatic calcification consists in the deposition of calcium in soft tissues incident to hyperparathyroidism, multiple myeloma, renal rickets, etc. Since the thoracic examples of this type of calcification occur peripherally and rarely, they do not often result in broncholithiasis.

(3) Dystrophic calcification is the deposition of calcium in necrotic, inflamed or degenerated tissue and constitutes the most common mechanism responsible for the occurrence of broncholithiasis.

*Pathology:* The mechanisms underlying the above have never been definitely established although general and local hypercalcemia, local changes in pH and toxic or idiopathic factors have been cited. By whatever process

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it occurs, broncholith formation results in an end product whose chemical composition is similar to that of bone. The main constituents of stones are calcium carbonate and calcium phosphate in essentially the ratio existing in bone. The factors which precipitate the migration of the calcifications are unknown although Head and Moen<sup>3</sup> have suggested that the cause is nontuberculous infection. Auerbach<sup>1</sup> suggests erosion of the bronchial wall as a result of continuous respiratory movements.

The stones are irregular, gray-white and of a few millimeters in dimensions (pigmentation, particularly secondary to anthracosis, occurs). They usually occur in the right lung and particularly in association with the right upper lobe. Schmidt<sup>7</sup> attributes this to the greater number of lymph nodes on the right, especially numerous in the region of the upper lobe bronchus.

*Symptoms:* The pathognomonic symptom of broncholithiasis is the expectoration of a stone. There is no characteristic clinical picture. At one extreme is the patient who is discovered at autopsy to have bronchial calculi although known to have been symptom free during life. At the other is the patient who constitutes a medical emergency because of chest pain or hemoptysis. One need only recall that broncholiths are foreign bodies to predict the symptoms they can cause.

Cough is an almost universal symptom. At first dry and hacking, it becomes productive of mucoid material in increasing amounts as bronchial irritation mounts. With partial obstruction and infection, the sputum becomes purulent.

Hemoptysis occurs in most cases, usually to a minimal degree. On occasion, transfusion or surgery may be indicated.

Pain was present in approximately one-half of all reported cases. It is usually retrosternal and of a pleuritic or tearing nature.

Fever, chills, weight loss, wheezing, dyspnea and other symptoms indicative of pneumonitis, abscess, bronchiectasis, atelectasis and empyema have been reported.

*Physical Findings:* The only abnormal physical findings are those arising directly or indirectly from hemorrhage or bronchial obstruction. Anything from a wheeze to atelectasis may be noted.

*Roentgenography:* Calcification in the tracheobronchial lymph nodes or in the lung fields proper is the usual roentgenographic picture. Secondary complications will be accompanied by their characteristic roentgenographic changes. Laminography may be of value. Schmidt<sup>7</sup> has called attention to the triangular area of pulmonary collapse at whose centrally located apex is noted an area of calcification.

*Bronchoscopy:* Because of the presenting clinical picture, most patients with symptomatic bronchial calculi are subjected to bronchoscopy. The endoscopist usually discovers ulceration or granulation tissue, frequently with the calculus buried within the tissue. The involved area may be inaccessible and thoracotomy necessary. Nevertheless, bronchoscopy remains a valuable diagnostic procedure.

*Treatment:* In many of the cases the broncholiths are spontaneously

evacuated, removed by endoscopy or expectorated after instrumentation and dilatation. A few cases must be treated surgically because of existing complications. Finally, because of the laudible increase in exploratory thoracotomies in those cases in which an obscure lesion is noted, it is anticipated that more bronchial calculi will be uncovered and treated in this fashion. Since the underlying pathology fosters recurrence, it is advisable to leave as much functioning lung tissue as possible. Appropriate medical therapy is administered when indicated for the secondary complications.

*Case Report:* This 58 year old male fisherman was admitted to the hospital on March 31, 1952, with the roentgenographic and bacteriologic diagnosis of pulmonary tuberculosis, active. He gave a history of hospitalization from 1936 to 1942 because of pulmonary tuberculosis for which he was treated with bed rest and phrenicotomy. Subsequent to this initial hospitalization he worked full time at his trade, remaining asymptomatic until the summer of 1951 when he noted the gradual onset of weight loss, weakness, easy fatigability, cough, hemoptysis and night sweats. Although evaluation in January of 1952 revealed the presence of active pulmonary tuberculosis, he deferred hospitalization until March 31 of that year.

Physical examination on admission revealed a thin male who appeared chronically ill. Temperature was 97.6 degrees F. The pulse was 100. The blood pressure was 140 mm. Hg. systolic and 100 mm. Hg. diastolic. Height was six feet. Weight was 145 pounds. With the exception of a long-standing neurodermatitis, the abnormal physical findings were limited to the chest. There was noted a visible and palpable lag of the left hemithorax with increased vocal fremitus and bronchial breathing over the left subapical region posteriorly.

Roentgenogram of the chest revealed an extensive exudative lesion in the left upper lobe with cavitation. Numerous calcifications were noted in the lung fields and mediastinum adjoining the left hilus. The sputum contained many tubercle bacilli on direct smear and culture.

Subsequent to admission the patient was placed on strict bed rest. Para-aminosalicylic acid was started at a dosage of 12 Gm. per day. However, because of gastrointestinal symptoms, the latter was reduced to approximately 8 Gm. per day. Because of persistence of symptoms which prompted admission, he was given 1 Gm. of streptomycin per day for 10 days. There immediately followed notable clinical improvement. Subsequent thereto 1 Gm. of streptomycin three times per week was given. Under the described regimen he exhibited definite limited clinical improvement. Bronchoscopy revealed only the presence of yellow mucopurulent material in the left upper lobe bronchus. Bronchography failed to reveal definite evidence of bronchiectasis. In December 1952 he was subjected to pneumonectomy and later to thoracoplasty. The former procedure was, technically speaking, extremely difficult. Examination of the mediastinum during surgery failed to reveal any abnormality in number or character of the lymph nodes.

Two months after admission to the hospital he casually mentioned the expectoration of a stone which he presented to the examiner. This was grayish white, irregular and of several millimeters in dimensions. Its consistency was of bone. Questioning revealed that between January and March 1952 on three occasions he expectorated a stone. Each episode began with an increase in the frequency and severity of the already present cough as well as increased expectoration of mucopurulent material. At no time was there hemoptysis, pain nor other attendant symptoms of any sort.

Pathologic examination of the removed lung revealed fibrocaceous tuberculosis with multiple cavitation. Search was specifically made for broncholiths and sources thereof. None was found. He is making an uneventful recovery from surgery.

### Discussion

Broncholiths most commonly arise within intrathoracic tissues previously infected with tubercle bacilli. Surprisingly, their appearance during active pulmonary tuberculosis has been noted infrequently. Stivelman<sup>8</sup> reported one case in 5,000 active tuberculars while Zahn<sup>10</sup> noted a single case among 4,000 such patients. Pritchard<sup>6</sup> reported two cases in 7,000 patients with tuberculosis. Since many tuberculous patients with active disease have had previous episodes of activity, one would expect a high incidence of broncholithiasis in them. Moreover, they are susceptible to secondary infection which Head<sup>3</sup> contends precipitates the migration of stones. In all probability, such an increased incidence of broncholithiasis exists in active tuberculosis but has not been reported. More frequent direct questioning of patients with regard to the expectoration of stones should confirm this as should future reports in the literature.

### SUMMARY

Broncholithiasis has been discussed and the literature briefly reviewed. A case of broncholithiasis occurring in active tuberculosis is reported. It is suggested that the incidence of such cases is greater than recorded. More frequently the patient should be specifically queried regarding this phenomenon.

### RESUMEN

Brevemente se revist la literatura y se discute la broncolitiasis. Se refiere un caso de broncolitiasis que ocurrió en tuberculosis activa. Se sugiere que incidencia de tales casos es mayor de lo que se ha referido. Debe ser investigad o mas frecuentemente el enfermo en relación con esta posibilidad.

### RESUME

L'auteur met en discussion un syndrome de broncho-lithiase et passe en revue rapidement la littérature concernant ce sujet. Il rapporte une observation de broncho-lithiase survenue au cours d'une tuberculose évolutive. Il lui semble que la possibilité de tels cas est plus importante qu'on ne le rapporte habituellement. On devrait plus souvent rechercher ce phénomène par l'interrogatoire des malades.

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# Training in Cardiology

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The evergrowing ramification of present day medical specialization though it has raised the quality of medical care, has also produced men who "know more and more about less and less." The field of heart and circulation alone nowadays requires subspecialists in peripheral vascular disease, in hypertension, in congenital heart disease, in pediatric cardiology; it has produced electrocardiographers, vectorcardiographers, ballistocardiographers, hemodynamic clinicians, electrolyte and renal physiologists. It is a rare institution indeed where, in cardiology alone, an attempt is made to provide the proper balance of all forces and it is a rarer person yet whose vision has escaped this specialistic myopism in cardiology. If he has, he is generally frowned upon as a jack of all trades who would have done better to continue his earlier studies on the left atrial electrocardiogram. This trend toward specialism and subspecialism is not confined, of course, to this field but is general. It has its origin in the ever expanding horizon of medical knowledge. Almost by necessity the present requirements of medical knowledge leave the student graduating from medical school in a bewildered state of half education and with his training largely incomplete.

Postgraduate instruction in cardiology, therefore, begins with graduation from medical school. Even at best little more has been accomplished during the preceding four years than to teach the techniques of examination and the significance of history taking and of physical signs. There has been some integration of laboratory procedures with a general tendency of over-evaluation of the latter with respect to the former both by the teacher and by the student. The training in basic medical science has largely been forgotten and rightly there has been little emphasis on treatment at this time.

The first step in postgraduate training is achieved during the internship. In this connection, a rotating internship of 12 months particularly in a private hospital is often of no value since it provides little more and often less than an undergraduate clerkship. Rotating internships in large charity institutions, on the other hand, are generally more rewarding because of the considerable responsibilities usually placed upon the ward physician and his frequent need for independent decisions. A straight 12 months internship in medicine is to be preferred, if possible at a teaching hospital, because it lays the background for medical experience and because it teaches practical therapy based on fundamental physiologic and biochemical prin-

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ciples. Teaching the "Art of medicine" can be learned on the ward as well and as effectively as in a private room, and the clinical aspects of heart disease and bedside diagnostic techniques can be refined and enlarged by conscientious visiting staffmen to an equal or better degree than by the overburdened and hurried practicing physician.

The second step consists of acquainting the budding internist who by now has advanced to an assistant residency with the special procedures in the diagnosis of cardiovascular disorders. By now, he has had some exposure to cardiac radiology, electrocardiography and to a catheterization laboratory, to name the most important tools. The practice of attending short intensive courses in special subjects (such as electrocardiography) is to be discouraged except as a refresher for the already experienced since even the best of these are quite ineffective on any level and often lull the participant into a false sense of security. After some exposure to these techniques during the assistant residency, one full year spent in a cardiovascular laboratory as an active member of the team will usually provide an adequate background if the laboratory can offer experience in all major fields of cardiology, and if the instruction stresses basic physiological principles. If such a laboratory is directed on a strictly clinical level, additional training in a department of physiology, biophysics or perhaps pharmacology becomes essential. As a rough guide, six months should be spent in what might be termed applied electrophysiology, and six months in the pursuit of hemodynamic studies. In order to obtain a balanced training period, it is important that the student maintain a continuous contact with general medicine throughout this year, by working one or two half days in a general medical clinic, by attending lectures and seminars on a variety of clinical and preclinical subjects, not concerned with cardiology, and whenever possible by actively participating in medical ward teaching. Further clinical bedside experience usually comes as the natural consequence by contact with the senior men of this specialty group.

At the end of this year such a fellow has just become a useful member of the unit and more likely than not he will be asked to continue. If he does, he must try his hand in active independent investigative pursuits, and now the machinery is set in motion which will test him as a future clinical research worker. He often decides, however, to return to another year of medical residency and then he takes the "plunge" into practice.

The third phase continues for the rest of his life in a permanent struggle to keep abreast of the ever changing aspects of the field. Reading a journal is out of fashion and very few practicing cardiologists take the leisure to even digest the journals of their own special field of interest. Since time is short he is best advised to read one journal well, and this should be one devoted to internal medicine. Important advances of lasting value will sooner or later find their way into this channel.

Once or twice a year he should attend a formal course or a formal meeting. Such events generally feature formal lectures or "papers," round table discussions, and occasionally practice or laboratory sessions. Of these, the formal papers are usually least instructive unless they are presented by

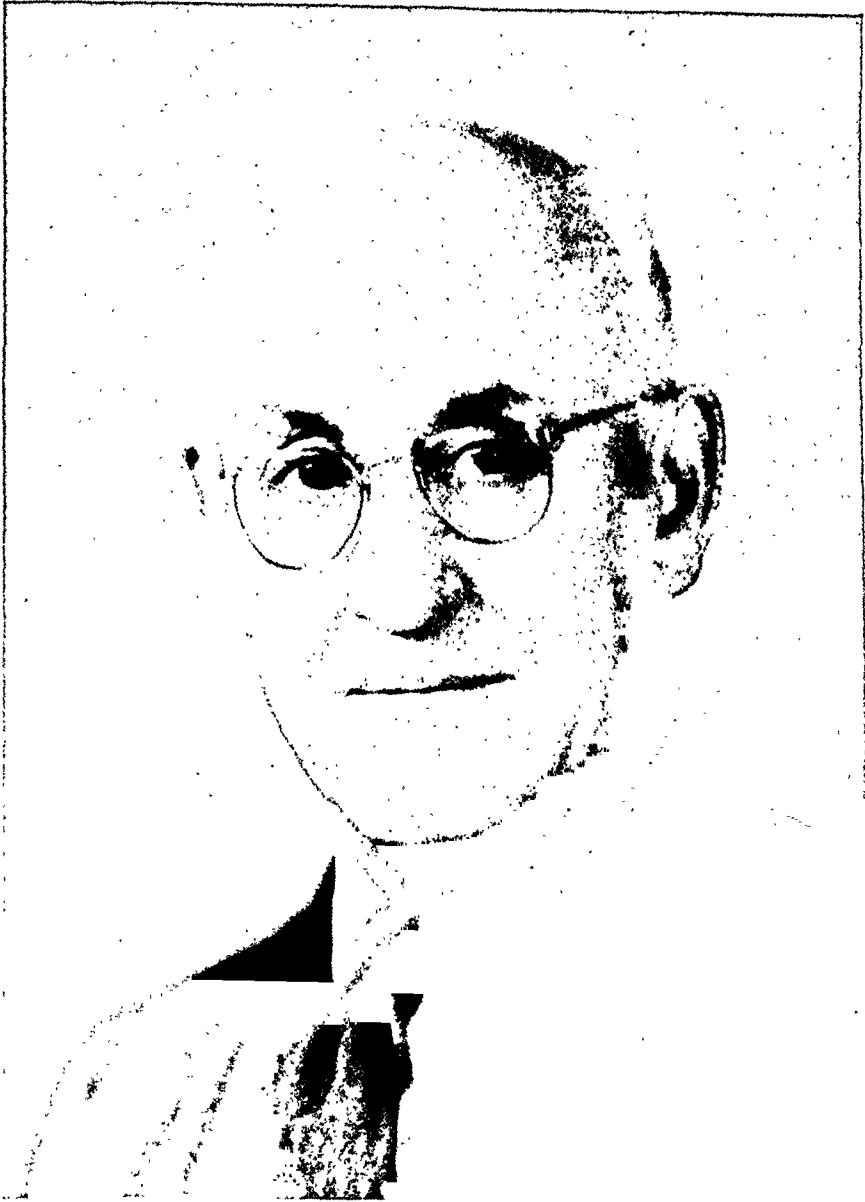
skillful "professional" teachers. They are likely to be monotonous and are confined to one man's view. On the other hand, round table discussions—often with question and answer periods—are generally more rewarding, since a topic can be viewed from all angles. This usually results in a satisfactory condensation of the present day knowledge concerning the subject of the discussion, particularly if the participants are chosen from a variety of disciplines. Such periods should be long, to allow for all possible contingencies and they are only effective if all members of the panel clearly understand the subjects and the ramifications that are to be covered. Frequent interplay among the discussors themselves or with discussors in the audience is desirable. Too frequently, such meetings bog down in irrelevant details, the result of poor planning. With audience participation such sessions can be far more instructive than formal presentations occupying a similar block of time.

The specialists who really desire information concerning present day investigative activities should not look to college meetings but should attend the fall or winter session of the Western, Southern, or Central Societies for Clinical Investigation, or to the spring meetings of the American Society for Clinical Investigation and the American Association of Physicians, all of which are open to everyone. Here the results of up to date clinical and experimental research are being presented in short presentations which in general are far more original and rewarding than formal, often already second hand orations at various college meetings. The ultimate of detailed specialistic information is available at the annual meeting of the Federation of American Societies for Experimental Biology ("Federation Meetings"), or the fall meeting of their component societies (Physiological Society, Society for Experimental Therapeutics, etc.).

In summary, postgraduate training in cardiology should focus on (a) a year or two of full time training in a cardiovascular laboratory, equipped to provide instruction in applied electrophysiology, (b) postgraduate course work with emphasis on round table discussion, (c) short intensive training sessions in small groups, covering a subject completely by lecture-demonstration and by practice.

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1954 - 1955



Dr. Hudson, born in Jasper, Arkansas, February 23, 1891, received his preliminary education at the public schools in Newton County, Arkansas and graduated from high school at Sedalia, Missouri. He entered Washington University, St. Louis, Missouri where he received his Bachelor of Science Degree (1918), Doctor of Medicine Degree (1920), and Master of Science Degree in Medicine in 1922. Dr. Hudson served as Interne and Resident at the Royal Victoria Hospital in Montreal, Canada on the service of Dr. Edward Archibald. He came to Detroit in 1923 as a member of the staff of the Henry Ford Hospital (with Dr. Roy McClure) and served on the teaching staff of the Ford Hospital School of Nursing. He took special courses at Trudeau School, Saranac Lake, the Chevalier Jackson

Course at Philadelphia, and made a tour of European Clinics during the 1920's.

He entered the private practice of thoracic surgery including endoscopy in 1925, being one of the first to limit his practice thereby setting thoracic surgery apart from general surgery and emphasizing it as a specialty. Dr. Hudson organized one of the first clinics for thoracic surgery in the State of Michigan at the Grace Hospital in Detroit heading the department as Chief of the Division of Thoracic Surgery from 1925 to 1951 (Retired) and continues as a consultant in thoracic surgery. From the beginning, he and Mrs. Hudson, who is a registered nurse, have worked together as a team in the operating room and at medical meetings throughout the world, he in the surgical aspect and she in the study of nursing principles of which she has been an active teacher.

Among his other hospital affiliations he is Chief Surgeon at Oakland County Tuberculosis Sanatorium, Pontiac, Michigan; Attending Surgeon, Head of the Department of Surgery at the Chest and General Hospital of Detroit (formerly the Detroit Tuberculosis Sanatorium); Consultant in Thoracic Surgery at North End Clinic, Wayne County General Hospital, on the Courtesy Staff of the Henry Ford Hospital, and a number of other institutions.

His past and present teaching experience and affiliations include grade school, Newton County, Arkansas; State Teachers Normal, Emporia, Kansas; Assistant and Instructor in Bacteriology and Pathology at Washington University, St. Louis; Associate Professor of Clinical Surgery at Detroit College of Medicine and Surgery and Wayne University School of Medicine (retiring 1946); Extramural Lectures at the University of Michigan School of Medicine; and lectures on thoracic surgery including endoscopy to the student nurses of Grace Hospital, Detroit.

Dr. Hudson has been associated with the American College of Chest Physicians as a Fellow and member of the Board of Regents since its very early days. He presided as the permanent chairman of the scientific section at both the First International Congress on Diseases of the Chest in Rome, Italy, in 1950 and at the Second International Congress on Diseases of the Chest in Rio de Janeiro, Brazil, in 1952. He holds honorary memberships in the St. Louis Medical Society and Sociedad Peruana de Tisiologia (Lima, Peru); Miembro Adherent, Sociedad Argentina de Cirugia Toracica (Buenos Aires). He delivered the 2nd Howard Lillenthal Memorial Lecture of the New York State Chapter, and the 1st Charles M. Hendricks Memorial Lecture of the Texas Chapter of the College.

He is a member of the Board of Directors of the Common Cold Foundation and other memberships in medical societies include the American Medical Association, Michigan State Medical Society, Wayne County Medical Society, Michigan Trudeau Society, Michigan State and National Tuberculosis Associations; Detroit Academy of Surgery; a Fellow of the American College of Surgeons, the American Association for Thoracic Surgery and the American Bronchoesophagological Society. A Founder-Member of American Board of Thoracic Surgery (Certified); the American Board of Surgery (Certified); and the International Bronchoesophagological Society.

Non-Medical memberships include the Christian Church, Rotary International, Detroit Board of Commerce, Detroit Yacht Club, City Farmers Club of Detroit, Save the Children Federation (Board of Directors, National Organization); a member of the advisory Council U. S. Department of Agriculture, South Forest Experimental R-SS Research Program; and the Northwest Pasture Improvement Group, Arkansas (Founder Member). He is a member of all York Rite Bodies and the Scottish Rite Bodies in Masonry and the Shrine and is the Grand Royal Arch Captain of the Grand Chapter of Royal Arch Masonry of Michigan.

Dr. and Benta Hudson were married June 17, 1920 and have two sons, both married: William Andrew Hudson, Jr. and his wife Margaret, who live in Oklahoma City; and John Wallace Hudson and his wife Barbara and their two children William and Frances, who live on the Old Hudson Homestead near Jasper, Arkansas known as "Hudsonakers".



# Third International Congress on Diseases of the Chest

BARCELONA, SPAIN, OCTOBER 4 - 8, 1954

The Third International Congress on Diseases of the Chest sponsored by the Council on International Affairs of the American College of Chest Physicians and presented under the Patronage of the Spanish Government, will be held in Barcelona, Spain, October 4 through 8, 1954. We are pleased to present on the following pages the preliminary scientific program for the Congress, prepared under the chairmanship of Dr. Andrew L. Banyai, Milwaukee, Wisconsin. More than two hundred scientific papers covering all aspects of heart and lung disease will be presented by speakers from forty-one countries throughout the world.

In addition to the following formal presentations there will be panel discussions and motion picture sessions on diseases of the chest. The final program is being prepared in Barcelona with summaries translated into the four official languages of the Congress, i.e., Spanish, French, German and English.

His Excellency Francisco Franco is serving as the Honorary President of the Congress and other officers are Dr. Luis Rosal, President, Dr. Cristobal Martinez, the Marquis de Villaverde, Vice-President, and Dr. Anthony Caralps, Secretary General. It is most important that everyone planning to attend the Congress is registered at the office of the Secretary General, Dr. Caralps, *Corcega 393, Barcelona, Spain*, in order that each participant will receive, upon arrival in Barcelona, his official documents and invitations to the scientific sessions and social functions. It is therefore requested that those members who have not yet registered with Dr. Caralps, please do so at once, *by air mail*.

## PRELIMINARY PROGRAM

TUESDAY, OCTOBER 5, 1954 — HALL A

### *Carcinoma and Other Tumors*

- "Uncommon Intrathoracic Tumors," Anthony Caralps Masso, Barcelona, Spain
- "The Frequency of Tumors of the Respiratory System,"  
Giovanni L'Ellore, Rome, Italy
- "The Early Diagnosis of Bronchial Carcinoma,"  
H. W. Knipping, Koln-Lindenthal, Germany
- "Pulmonary Carcinoma in Printing Workers," Erik Ask-Upmark, Upsala, Sweden
- "Diagnostic and Therapeutic Results in 1,000 Cases of Bronchogenic Carcinoma,"  
J. Swierenga, Utrecht, Netherlands
- "Diagnosis and Differential Diagnosis of Tuberculosis and Carcinoma by  
Pleuroscopy," Anton Sattler, Vienna, Austria
- "Bronchial Adenomas," G. Manresa Formosa, Barcelona, Spain
- "Tumors of the Thymus," Roger Touraine, Lyon, France
- "Results of Surgical Treatment of Cancer of the Esophagus,"  
J. C. Rudler, Paris, France

### *Hydatid Disease*

- "Hydatid Cyst of the Lung, Surgical Treatment of 150 Cases,"  
Jorge Alberto Taiana, Buenos Aires, Argentina
- "Hydatid Disease of the Lung," Sinasi Guchan, Istanbul, Turkey

### ***So-Called Hypertrophic Emphysema***

"Pathogenesis and Treatment of So-Called Hypertrophic Emphysema,"  
Andrew L. Banyai, Milwaukee, Wisconsin, U.S.A.

"Pulmonary Ventilation and Circulation in Chronic Pulmonary Emphysema of the Lung," Karl Vuylsteek, Ghent, Belgium

"Emphysema in the Tuberculosis Clinic," O. Garcia Rosell, Lima, Peru

### ***Cystic Disease of the Lung***

"Anatomical Aspects of Congenital Cysts of the Lung,"  
Jose Reventos, Barcelona, Spain

"Air Cysts of the Lung," Nicola Sanguigno, Palermo, Italy

"Vanishing Lung," H. Wamsteker, Bloemendaal, Netherlands

### ***Miscellaneous Subjects***

"Oil Granuloma of Lung (Lipoid Pneumonia)," M. P. Susman, Sydney, Australia

"Simultaneous Bilateral Spontaneous Pneumothorax,"  
Jose Turell Guma, Barcelona, Spain

## **TUESDAY, OCTOBER 5, 1954 — HALL B**

### ***Cardiovascular Diseases***

"The Surgical Aspects of Patent Ductus Arteriosus,"  
George Mason, Newcastle-upon-Tyne, England

"Bronchiectasis," Nicolaas G. M. Orie, Groningen, Netherlands

"Physiopathology of Mitral Stenosis," I. Balaguer-Vintro, Barcelona, Spain

"Surgical Treatment of Congenital and Acquired Heart Diseases,"  
Decio Ferreira, Lisbon, Portugal

"Ligation of the Inferior Vena Cava Prior to Commissurotomy,"  
Rodolfo Redi, Bari, Italy

"The Status of Cardiovascular Surgery in Cuba,"  
Antonio Rodriguez Diaz, Havana, Cuba

"Surgical Treatment of Inter-auricular Septal Defects,"  
Jose Paravisini Parra, Barcelona, Spain

"Massive Occlusive Auricular Thrombosis After Mitral Commissurotomy and the Prophylactic Administration of Anticoagulants Following Cardiac Surgery,"  
A. P. Naef, Lausanne, Switzerland

"Comparison Between the Primary Results, Late Results and Complications of Valvulotomy for Mitral Stenosis," Helge B. Wulff, Malmo, Sweden

"Surgical Results of Mitral Commissurotomy,"  
Isidro Perianes, Buenos Aires, Argentina

### ***Tomography***

"Pulmonary Tomography, Experimental and Clinical Results,"  
Guido Pollitzer, Buenos Aires, Argentina

"Tomography of the Respiratory Tract," Andres Pursell Menguez, Barcelona, Spain

"Auxillary Tomography with Photo-Roentgenology,"  
Alvaro Urgoiti, La Coruna, Spain

### ***Cytology***

"Clinical and Cytologic Aspects of Pulmonary Enzymatic Therapy,"  
Seymour M. Farber, San Francisco, California, U.S.A.

"Cytological Patterns in Broncho-Pulmonary Disease,"  
A. A. Carabelli, Trenton, New Jersey, U.S.A.

"Systematic Chemical and Cytological Study of Intrathoracic Fluids,"  
Ricardo Vidal-Ribas, Barcelona, Spain

**WEDNESDAY, OCTOBER 6, 1954 — HALL B (Continued)**

"Limitations of the Operability of Cancer of the Lung,"  
Pierre Decker, Lausanne, Switzerland

"Posterior Mediastinal Malignant Tumor,"  
Thomas L. Dwyer, Mexico, Missouri, U.S.A.

"Bronchial Adenoma," Andre Meyer, Paris, France

"Cancer of the Lung Five Years After Radiation Therapy,"  
Juan Castillo, Havana, Cuba

***Hydatid Disease***

"Hydatid Cyst, Differential Diagnosis (Case Report),"  
Ramon Reventos Reventos, Barcelona, Spain

"Surgical Management of Pulmonary Hydatid Diseases,"  
Papken S. Mugrditchian, Beirut, Lebanon

***Bronchopulmonary Suppuration***

"Drainage Suction in Lung Abscess," Vincenzo Monaldi, Naples, Italy

"Surgical Treatment of Lung Abscess," A. Agusti, Barcelona, Spain

***Bronchiectasis***

"Bronchiectasis; Diagnosis and Treatment," M. Gili, Barcelona, Spain

"Bronchography in Children," Manuel Canizares, Quezon City, Philippine Islands

"The Prognosis of Bronchiectasis," A. M. Olsen, Rochester, Minnesota, U.S.A.

"The Surgical Treatment of Bronchiectasis; Statistical Results of 100 Cases,"  
Marcel Berard, Lyon, France

***Arteriovenous Aneurysm***

"Arteriovenous Aneurysm of the Pulmonary Vessels With Special Reference to the  
Importance of Oxymetry During Operation,"  
L. D. Eerland, Groningen, Netherlands

"Bilateral Arteriovenous Aneurysm of the Lung,"  
Dominique Raton, Besancon, France

**WEDNESDAY, OCTOBER 6, 1954 — HALL C*****Diagnosis***

"Pulmonary Changes in Septic Diseases," K. Bingold, Munchen, Germany

"Anatomical Basis of Hemoptysis," Jacinto Reventos Bordoy, Barcelona, Spain

***Prophylaxis and Treatment***

"Diagnosis, Prophylaxis and Treatment of Pulmonary Embolism,"  
Antonio Rodriguez Arias, Barcelona, Spain

"Aerosol Therapy of Chronic Non-Specific Infections of the Tracheo-Bronchial  
Tract," Jose Pablo Garcia Echevarria, Bilbao, Spain

"The Management of Esophageal Varices in Cirrhosis of the Liver in the Absence  
of Gastrointestinal Hemorrhage," Irving B. Brick, Washington, D. C., U.S.A.

***Tuberculosis***

"The Relationship Between Tonsillar Pathology and Pulmonary Ganglia,"  
Egidio Lenci, Rome, Italy

"The Role of Pneumothorax in the Treatment of Tuberculosis,"  
Fernand E. Cardis, Lausanne, Switzerland

"Wider Indications of Pneumolysis,"  
Harald Malluche, Falkenstein im Taunus, Germany

**WEDNESDAY, OCTOBER 6, 1954 — HALL C (Continued)**

- "Pneumoperitoneum—Indications and Results,"  
Juan Aguilera Mas, Barcelona, Spain
- "Thoracoplasty with Insufflation," Fernando Marques, Lisbon, Portugal
- "Residual Cavities After Thoracoplasty: A Therapeutic Study,"  
L. Luengo Serrano, Barcelona, Spain
- "The Morelli-Di Paola Thoracoplasty in the Surgical Treatment of Pulmonary Tuberculosis," Paul Kyrle, Vienna, Austria
- "Place of Thoracoplasty in Combination with Pulmonary Resection,"  
Alfred F. Brunner, Zurich, Switzerland
- "Indications and Limitations of Surgical Treatment of Bilateral Pulmonary Tuberculosis," Azio Valli, Forli, Italy
- "Segmental Resection in Pulmonary Tuberculosis. A Critical Study of Our First 100 Cases," A. Marmet, Colmar, France
- "Surgical Collapse Therapy in Tuberculous North African Mohammedans,"  
A. Levi-Valensi, Algiers, Algeria
- "Re-Resections for Complications After Resection Therapy for Pulmonary Tuberculosis," Jan K. Kraan, Appelscha, Netherlands
- "Late Results with Extraperiosteal Pneumolysis with Polystan,"  
Diego Garcia Alonso, Santander, Spain
- "Gas-Analytical and Broncho-Spirometrical Examinations of the Blood in Connection with Lung Surgery," Joachim Hein, Schleswig-Holstein, Germany
- "Resection in Pulmonary Tuberculosis," Alfred D. Dumont, Brussels, Belgium
- "Early Pulmonary Resection for Tuberculosis," Rui de Lima, Lisbon, Portugal
- "Miliary Tuberculosis Complicating Pregnancy,"  
Maurice D. Kenler, New Bedford, Massachusetts, U.S.A.
- "Inhibitory Effect of Tuberculous Pathologic Material Upon Isonicotinic Acid Hydrazide," M. Morellini, Rome, Italy.
- "The Use of Streptomycin, Isoniazide and PAS in Treatment of Advanced Pulmonary Tuberculosis," Carlos Maldonado, Puerto Montt, Chile

**THURSDAY, OCTOBER 7, 1954 — HALL A*****Bronchial Asthma***

- "Histological Studies of Aspirated Bronchial Secretions in Bronchial Asthma,"  
Raimundo Frouchtman Rager, Barcelona, Spain
- "Cardiovascular Origin of Asthma and the Treatment of Asthmatic Dyspnea,"  
Lino Businco, Rome, Italy
- "Pathogenesis and Etiology of Bronchial Asthma,"  
Santiago Millanes Marcos, Logrono, Spain
- "Bronchial Asthma: Etiology and Causal Therapy, Results of Respiratory Alteration," Walter Roloff, Leipzig, Germany
- "Bacteriology of Aspirated Bronchial Secretions in Bronchial Asthma,"  
Roberto Foz, Barcelona, Spain
- "The Study and Treatment of the Asthmatic Patient,"  
Harry L. Rogers, Philadelphia, Pennsylvania, U.S.A.
- "Characteristics of Asthma in the Canary Islands,"  
Camilo Rodriguez Cavilanes, Las Palmas, Spain
- "Treatment of Bronchial Asthma with Intravenous Novocain and Respiratory Exercises," R. A. Faris, Amman, Jordan
- "BCG Treatment in Asthma," Jose Oriol Anguera, Barcelona, Spain
- "The Prevention and Control of Bronchial Asthma by Continuous Postural Drainage," L. Bedford Elwell, Brisbane, Queensland, Australia

**THURSDAY, OCTOBER 7, 1954 — HALL A (Continued)**

"Bacterial Vaccine Therapy in Bronchial Asthma,"

Julian Lazaro Romeo, Bilbao, Spain

"The Treatment of Asthma," Louis Leopold Denis, Brussels, Belgium

***Surgery of the Thoracic Duct and Bronchi***

"The Cannulization of the Thoracic Duct in Humans: A Radiological and Physiological Study," Alfred Goldman, Beverly Hills, California, U.S.A.

"Plastic Tracheal and Bronchial Anastomosis,"

Eduardo Esteves Pinto, Porto, Portugal

"Intrathoracic Rupture of the Trachea and Major Bronchi,"

John V. Thompson, Indianapolis, Indiana, U.S.A.

"Closure of the Bronchus in Pulmonary Resections,"

M. C. A. Klinkenbergh, Utrecht, Netherlands

***Diagnosis***

"Mediastinography with Pneumomediastinum,"

Maurice Jacques Bariety, Paris, France

"Displacement of Heart and Large Vessels in Chronic Pulmonary Disease,"

Wladimir Griffel, Preston, England

"Diagnostic Interpretation of Basal Pulmonary Shadows,"

Jose Cornudella, Barcelona, Spain

"Rheumatoid Syndrome in Intrathoracic Lesions: Vagal Reflex or Not?,"

Jans L. Hansen, Copenhagen, Denmark

**THURSDAY, OCTOBER 7, 1954 — HALL B*****Tuberculosis***

"Migratory Pulmonary Infiltration with Eosinophilia of the Blood,"

Wilhelm Loeffler, Zurich, Switzerland

"Anatomico-Clinical Studies of Bronchial Tuberculosis in Pulmonary Resection,"

Juan Bta. Roset Coll, Barcelona, Spain

"Status of the Anti-Tuberculosis Campaign in the Philippines,"

Manuel Quisumbing, Sr., San Pablo City, Philippine Islands

"Present Status of Collapse Therapy in Pulmonary Tuberculosis,"

Benjamin P. Potter, Weehawken, New Jersey, U.S.A.

"Our Experience with 110 Cases of Extrapleural Pneumonolysis,"

Fernando Ma. Mugica Iza, Bilbao, Spain

"Intrapleural and Extrapleural Pneumolysis,"

Rlias Abdallah Sader, Beirut, Lebanon

"The Pathogenesis and the Surgical Treatment of Pulmonary Tuberculosis,"

Shinobu Miyamoto, Tokyo, Japan

"The Association of Intercavitary Aspiration and of Surgical Pneumothorax in the Treatment of Otherwise Desperate Cases,"

Maurizio Mendes, Jerusalem, Israel

"Critics on Monaldi Cavity Drainage and Maurer Tamponade in the Local Treatment of Tuberculosis Cavities," Ihsan Rifat Saber, Istanbul, Turkey

"Research on the Combined Use of Streptomycin and Isoniazid,"

L. Checcacci, Pavia, Italy

"Collective Critical Review of Current Therapy in Pulmonary Tuberculosis: A Study of 100 Participating Physicians with Analysis of Their Opinion,"

Harold G. Trimble, Oakland, California, U.S.A.

"Streptomycin and Isonicotinic Hydrazide in Pulmonary Tuberculosis,"

A. Omodei Zorini, Rome, Italy

**THURSDAY, OCTOBER 7, 1954 — HALL B (Continued)**

- "Anatomical Modifications of Tuberculous Lesions Treated with Chemotherapy,"  
J. F. Valiente, San Salvador, El Salvador
- "Intrabronchial Local Application of Antibiotics in the Management of Inert  
Pulmonary Cavities Treated with Collapse Therapy," Bruno Besta, Rome, Italy
- "Treatment of Fibrocaceous Lesions with Antibiotics, Tuberculin and Iodides,"  
Euro Torres Leon, Guayaquil, Ecuador
- "Clinical Observations of the Antituberculous Activity of Diphenyl Thiourea  
Compounds," Joseph A. Schwartz, San Fernando, California, U.S.A.
- "Active and Prophylactic Management of Tuberculosis in Pregnancy,"  
Irving Selikoff, Paterson, New Jersey, U.S.A.
- "Pulmonary Vascular Changes in Patients Treated with Antibiotics and  
Chemotherapy," Carlo Pana, Rome, Italy
- "The Changing Tuberculosis Control Program in the United States,"  
R. J. Anderson, Washington, D. C., U.S.A.
- "A Study of Factors Involved in Reactivation of Pulmonary Tuberculosis Over a  
Five Year Period Among Patients Discharged from Sanatoria as Arrested,"  
Oscar Feinsilver, Worcester, Massachusetts, U.S.A.
- "Post-Sanatorium Management for Tuberculosis,"  
Donald McKay, Buffalo, New York, U.S.A.
- "Comparative Study of a Dried and a Wet BCG Vaccine,"  
Toshieki Ebina, Sendai, Japan
- "The Experimental Comparison Regarding Development of Tuberculosis Infection  
with Normal Bacteria as Compared to Streptomycin Resistant Bacteria,"  
S. Gunella, Parma, Italy

**THURSDAY, OCTOBER 7, 1954 — HALL C*****Cardiovascular Diseases***

- "Hydatid Cysts of the Heart," Pablo Purriel, Montevideo, Uruguay
- "Optimism in Heart Disease," John F. Briggs, St. Paul, Minnesota, U.S.A.
- "Neuro-Hormonal Factors in Cardiac Pathology,"  
Wilhelm Raab, Burlington, Vermont, U.S.A.
- "Rehabilitation in Coronary Artery Occlusion,"  
R. W. Kissane, Columbus, Ohio, U.S.A.
- "Dextrocardia and Situs Inversus," Emil Bogen, Olive View, California, U.S.A.
- "Correlation Between Right Ventricular Hypertrophy and Direct Intracardiac  
Pressure," M. Torner-Soler, Barcelona, Spain
- "Further Studies With External Electrical Stimulation for Ventricular Standstill,"  
Elmer C. Rigby, Los Angeles, California, U.S.A.
- "Quinidine in Auricular Fibrillation,"  
Samuel A. Weisman, Los Angeles, California, U.S.A.

***Bronchostenosis***

- "On the Pathogenesis and Practical Importance of Bronchostenosis and Allied  
Chronic Abnormalities (Except in Tuberculosis and Tumor Cases),"  
Alf V. Westergren, Stockholm, Sweden
- "Bronchial Stenosis Caused by Parahilar and Mediastinal Calcification,"  
Mario Benvenuti, Rome, Italy

***Empyema***

- "Possibilities and Limitations of the Surgical Treatment of Chronic Empyema,"  
Giuseppe Zorzoli, Rome, Italy
- "Surgical Treatment of Non-Tuberculous Empyema," L. Gonzales, Barcelona, Spain
- "Decortication for the Treatment of Empyema," Felipe Margarit, Barcelona, Spain

THURSDAY, OCTOBER 7, 1954 — HALL C (Continued)

*Foreign Bodies in the Lung*

"The Diagnosis of Vegetal Foreign Bodies in the Lower Respiratory Tract,"  
Raymond Rosedale, Canton, Ohio, U.S.A.

"Latent Endo-Bronchial Foreign Bodies,"  
Jacinto Sanglas Casanovas, Barcelona, Spain

*Miscellaneous Subjects*

"Pulmonary Manifestations in Schistosomiasis,"  
E. Martinez-Rivera, Hato Rey, Puerto Rico

"Transparietal Extension of Pleuromediastinal Granulomas,"  
Paul J. L. Desaive, Liege, Belgium

"The Relation of Aetiology to Radiographic Appearance in Pneumonia,"  
John Crofton, Edinburgh, Scotland

"Middle Lobe Syndrome," A. Castella Escabros, Barcelona, Spain

"Pulmonary Lesions in Schistosomiasis," Jose Silveira, Bahia, Brazil

"Fibrothorax—Study and Therapy," F. Gonzalez Soler, Barcelona, Spain

FRIDAY, OCTOBER 8, 1954 — HALL A

*Tuberculosis*

"The Value of a Method of Areosol Bronchial Lavage for Obtaining Positive Cultures in Patients with Negative Sputa and Gastric Washings,"  
Eugenio Fernandez-Cerra, Hato Rey, Puerto Rico

"BCG Vaccination," Georges Georgakopoulos, Athens, Greece

"BCG Vaccination in Ceylon," George E. Ranawake, Colombo, Ceylon

"Pregnancy and Breast-Feeding in Cases of Tuberculosis,"  
Erik Hedvall, Uppsala, Sweden

"Pregnancy and Tuberculosis," Hollis E. Johnson, Nashville, Tennessee, U.S.A.

"The Treatment of Pulmonary Tuberculosis," Guiseppe Di Maria, Rome, Italy

"Tuberculin and Chemotherapy in Pulmonary Tuberculosis,"  
R. Y. Keers, Aberdeenshire, Scotland

"Diaphragm Exercise in the Prevention of Ventilatory Insufficiency,"  
Gosta Birath, Gothenburg, Sweden

"Chemotherapy in Patients with Pulmonary Tuberculosis of Apparently Unfavorable Prognosis," Albert Reginster, Liege, Belgium

"Streptomycin-Hydrazid Aerosol-Mist in Pulmonary Tuberculosis,"  
Ugo Paolantonio, L'Aguilla, Italy

"The Evolution of Tuberculosis in Chile," Hector Orrego Puelma, Santiago, Chile

"Streptomycin and Isoniazid Treatment of Miliary Tuberculosis of the Lung in Infants," Umberto Monaco, Rome, Italy

"Experience with Isoniazid in Pulmonary Tuberculosis—Public Health Viewpoint,"  
Irving Willner, Newark, New Jersey, U.S.A.

"Paradoxical Results of Incomplete Pneumothorax,"  
Rafael Serra Goday, Barcelona, Spain

"The Importance of Hilar Lymph Nodes in the Origin of Complications After Resection Surgery," Tomas Seix Miralta, Barcelona, Spain

"Indications for Surgery in Tuberculosis After Treatment with Antibiotics and Chemotherapy," P. G. Schmidt, Waldbreitbach, Germany

"Endobronchial Treatment of Blocked Cavities,"  
Raimundo Cornudella Mir, Barcelona, Spain

"Evolution and Present Status of Chemotherapeutics Tamponade of Pulmonary Cavities," Gustave Maurer, Zurich, Switzerland

**FRIDAY, OCTOBER 8, 1954 — HALL A (Continued)**

"The Limitations of Surgery in Pulmonary Tuberculosis,"  
Eugenio Morelli, Rome, Italy

"Tuberculosis Among Nurses," Jay Arthur Myers, Minneapolis, Minnesota, U.S.A.

**FRIDAY, OCTOBER 8, 1954 — HALL B*****Cardio-respiratory Function Studies***

"Circulatory Function Studies Prior to Thoracic Surgery,"  
Juan Vives Uno, Barcelona, Spain

"The Importance of Angio-Cardiography and Selective Angiopneumography in Surgery of the Heart and Lungs," J. Martins da Fonseca, Lisbon, Portugal

"Selective Angiography of Pulmonary Vessels as a Functional Test in Thoracic Surgery," Wilhelm Bolt, Cologne, Germany

"Comparative Value of Bronchspirometry and Angiopneumonography in the Functional Examination of Each Lung,"  
Raul F. Vaccarezza, Buenos Aires, Argentina

"Importance of Pulmonary Function Tests for Operative Indications in Chest Surgery," Carl B. Semb, Oslo, Norway

"The Effect of the Movements of the Diaphragm and Respiratory Function,"  
Rome, Italy

"Respiratory Function Tests in Thoracopulmonary Surgery,"  
Josef Verna, Cordoba, Argentina

"The Effects of Exercise on the Heart and Lungs,"  
Burgess L. Gordon, Philadelphia, Pennsylvania, U.S.A.

"Respiratory Function Studies in Granulomatous Diseases of the Lung with Miliary Type Involvement," Jean M. Verstraeten, Ghent, Belgium

"Ventilation of the Non-Collapsed Tuberculous Lung," Paul Sadoul, Nancy, France

"Oximetry and Carboximetry During Thoracic Operations and in Respiratory Functional Research," R. Brinkman, Groningen, Netherlands

***Diagnosis***

"Chest Disease in Institutions," Otto L. Bettag, Chicago, Illinois, U.S.A.

"The Value of Mass X-ray Surveys in Non-Tuberculous Diseases of the Chest,"  
Manoel de Abreu, Rio de Janeiro, Brazil

"Agenesis of the Lung," Agustin Amell-Sans, Barcelona, Spain

"Idiopathic Pulmonary Hemosiderosis," Bianco G. Mariana, Rome, Italy

"Bronchopulmonary Ossifications Identified on Surgical Intervention,"  
Henri Louis Le Brigand, Paris, France

"The Extrathoracic Causes of Cough,"  
Barney M. Kully, Los Angeles, California, U.S.A.

"Congenital Malformations," Francisco Perez Marrero, Las Palmas, Spain

"Anatomical Aspects of Pulmonary Atelectasis,"  
Enrique Bieto Reiman, Barcelona, Spain

"Pneumoperitoneum in Combination with Pneumothorax in the Diagnosis of Thoraco-Abdominal Conditions," Attilio DeMartini, Genoa, Italy

**FRIDAY, OCTOBER 8, 1954 — HALL C*****Carcinoma and Other Tumors***

"The Necessity of Using Every Possible Technique in the Exact Diagnosis of Cancer of the Bronchus," Andre Soulas, Paris, France

"Possibilities and Limitations of Bronchial Aspiration in the Diagnosis of Lung Tumors," Francisco Coll Colome, Barcelona, Spain



**FRIDAY, OCTOBER 8, 1954 — HALL C (Continued)**

- "Incidence and Location of Tumors of the Respiratory Tract,"  
Onofrio Ceino, Rome, Italy
- "Hypertrophic Osteoarthropathy in Association with Bronchial Carcinoma,"  
Thomas Semple, Glasgow, Scotland
- "A Pleural Type of Primitive Lung Cancer," G. Babolini, Naples, Italy
- "Prolonging Life in Pulmonary Cancer,"  
Richard H. Overholt, Brookline, Massachusetts, U.S.A.
- "Early Diagnosis of Cancer of the Lung—Clinical Aspects,"  
Edgar Mayer, New York, New York, U.S.A.
- "Early Diagnosis of Cancer of the Lung—Bronchoscopic Aspects,"  
Arthur J. Cracovaner, New York, New York, U.S.A.
- "Pulmonary Manifestations of Adenomatosis," Enrico Fasano, Bologna, Italy
- "Neoplasms of the Esophagus," Isidro Triadu Castellis, Barcelona, Spain
- "Benign Intrathoracic Tumors," B. G. Begin, Montreal, Quebec, Canada
- "Bronchiogenic Carcinoma and Tuberculous Lymph Node Calcifications,"  
Paul Galy, Lyon, France

***Hydatid Disease***

- "Experimental Studies in Hydatid Disease of the Lung," Jose Abello, Madrid, Spain
- "Surgical Treatment of Hydatid Cyst of the Lung,"  
Emir Cesar Chehab, Beirut, Lebanon
- "Status of the Surgical Treatment of Hydatid Cyst of the Lung,"  
Tomas Lorenzo Fernandez, Barcelona, Spain

***Bronchopulmonary Suppuration***

- "Clinical Aspects and Frequency of Bronchopulmonary Suppurations in Private Practice," Gumersindo Sayago, Cordoba, Argentina
- "Endobronchial Treatment of Lung Abscess," Jose Palou Llaudet, Barcelona, Spain

***Loeffler's Syndrome***

- "On the Relationship Between So-Called Transitory Pulmonary Infiltration and Primary Atypical Pneumonia," Shinnosuke Fujita, Tokyo, Japan
- "Transient Pulmonary Infiltration," P. Baringo Alcolea, Barcelona, Spain

***Sarcoidosis***

- "Mediastino-Pulmonary Localization of Besnier-Boeck-Schaumann Disease,"  
Gennaro Costantini, Naples, Italy
- "Clinical Aspects of Sarcoidosis of the Lung,"  
Ludwig Heilmeyer, Freiburg, Germany
- "The Diagnosis of Sarcoidosis," Hugh G. Whitehead, Baltimore, Maryland, U.S.A.

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**OTHER INTERNATIONAL CONGRESSES**

XIII Conference, International Union Against Tuberculosis  
Madrid, Spain, September 26 - October 2, 1954.

8th General Assembly, World Medical Association  
Rome, Italy, September 26 - October 2, 1954.

Third Congress, International Bronchoesophagological Society  
Lisbon, Portugal, October 10 - 13, 1954.

Look for the

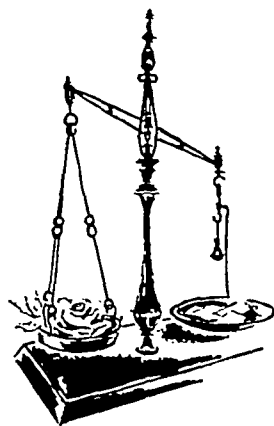
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## MEDICAL SERVICE BUREAU

### POSITION AVAILABLE

Assistant Medical Director wanted for 100 bed tuberculosis hospital, North American graduate, salary \$8,500, complete maintenance. Apply Medical Director and Superintendent, District One Tuberculosis Hospital, Madisonville, Kentucky.

### CALENDAR OF EVENTS

#### NATIONAL AND INTERNATIONAL MEETINGS

Third International Congress on Diseases of the Chest

Council on International Affairs

American College of Chest Physicians

Barcelona, Spain, October 4-8, 1954.

Interim Session, American College of Chest Physicians

Delano Hotel, Miami Beach, Florida, November 28-29, 1954.

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#### POSTGRADUATE COURSES

9th Annual Postgraduate Course on Diseases of the Chest  
Hotel Knickerbocker, Chicago, Illinois, October 18-22, 1954.

Postgraduate Course on Diseases of the Chest  
Bunts Institute, Cleveland, Ohio, October 27-28, 1954.

7th Annual Postgraduate Course on Diseases of the Chest  
Hotel New Yorker, New York City, November 8-12, 1954.

8th Annual Postgraduate Course on Diseases of the Chest  
Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, Spring, 1955.

### ANNOUNCEMENTS

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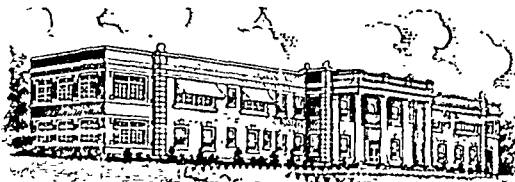
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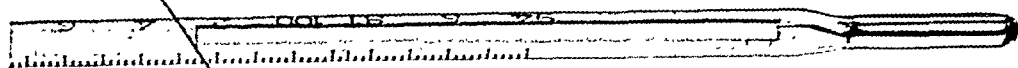
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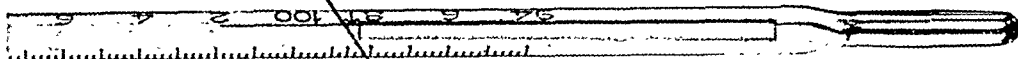
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1. Filippin, H. F.: Philadelphia Med. 49:733 (Jan. 30) 1954.
2. Glatt, M., and Ross, S.: Antibiotics & Chemotherapy 4:395 (Apr.) 1954.

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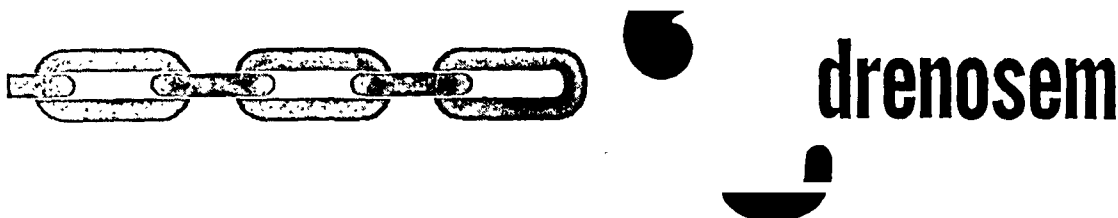
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\*Sherber, D. A.: The Control of Bleeding, Am. J. Surg. 86:331 (Sept.) 1953.



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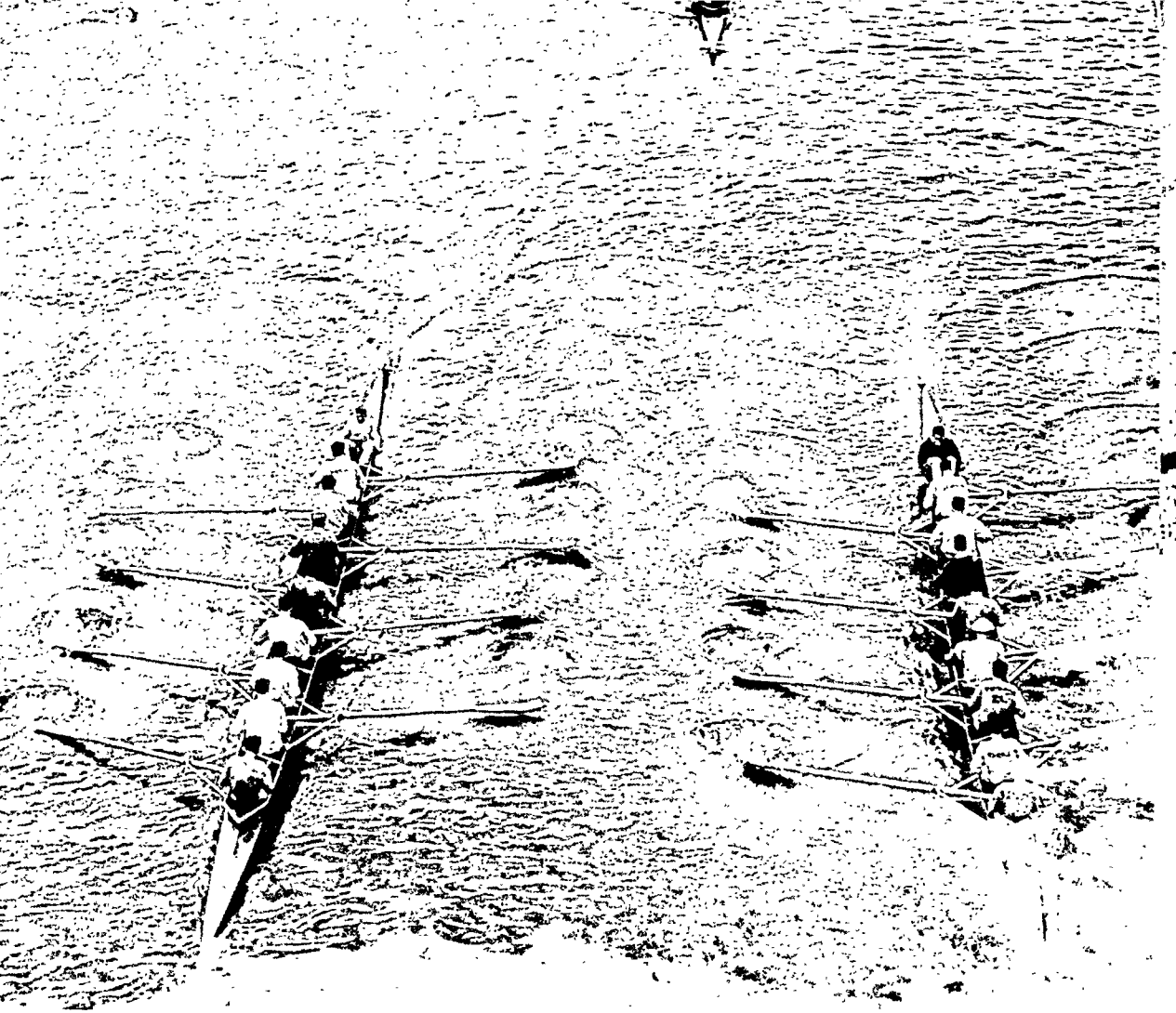
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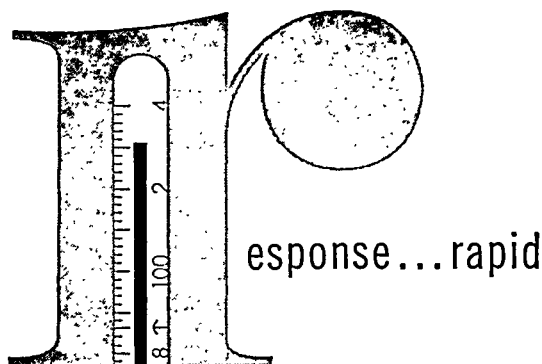
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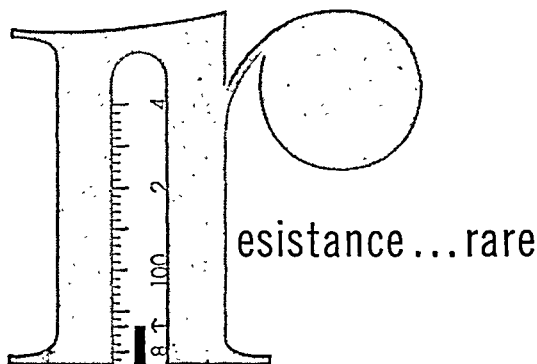


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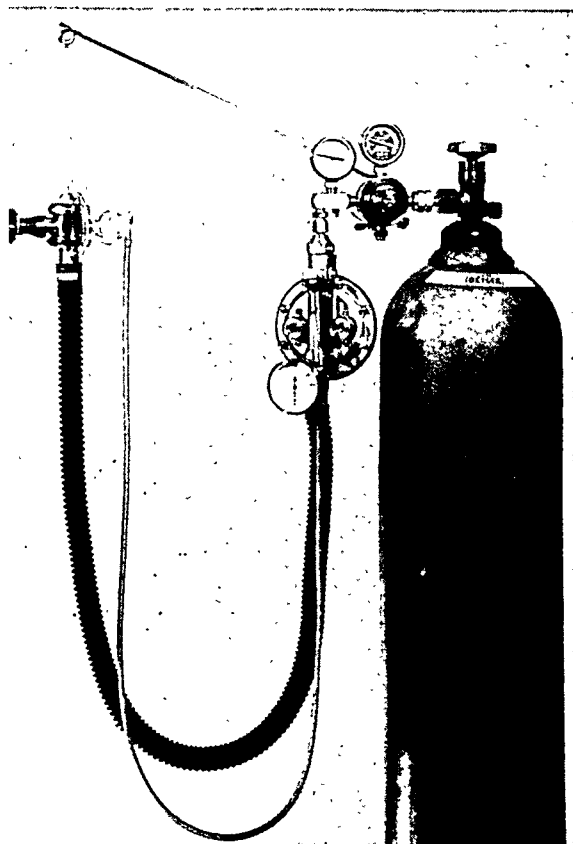
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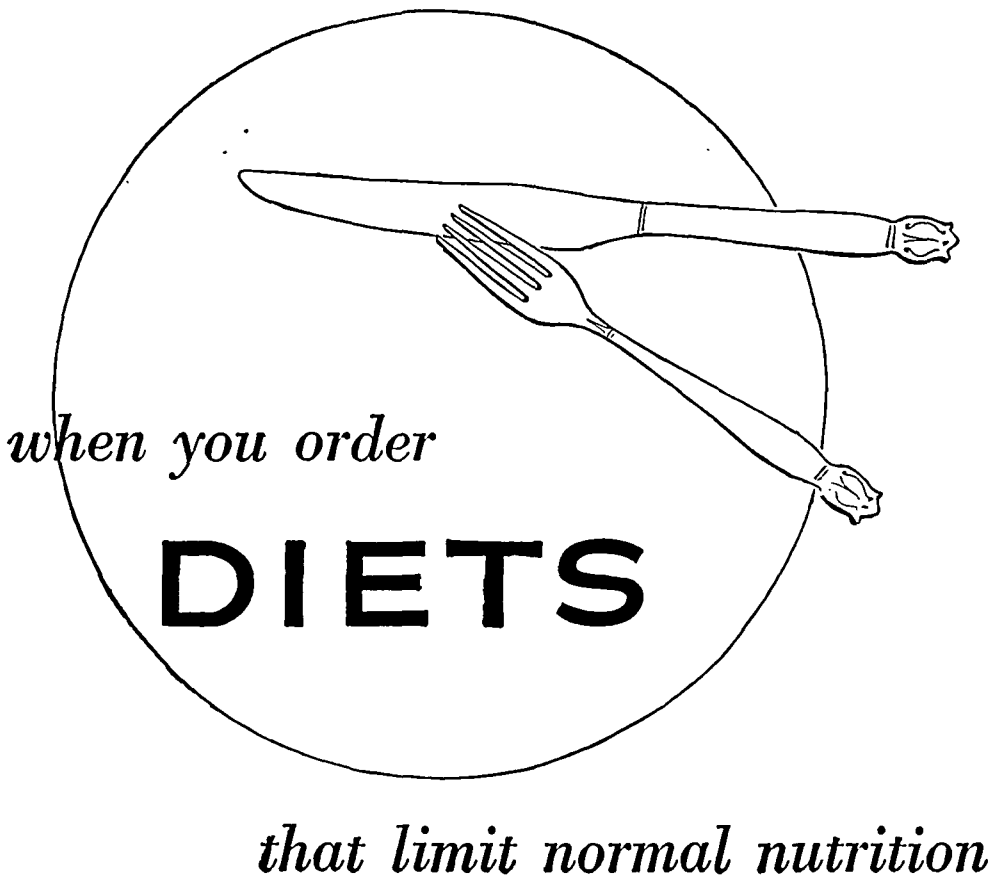
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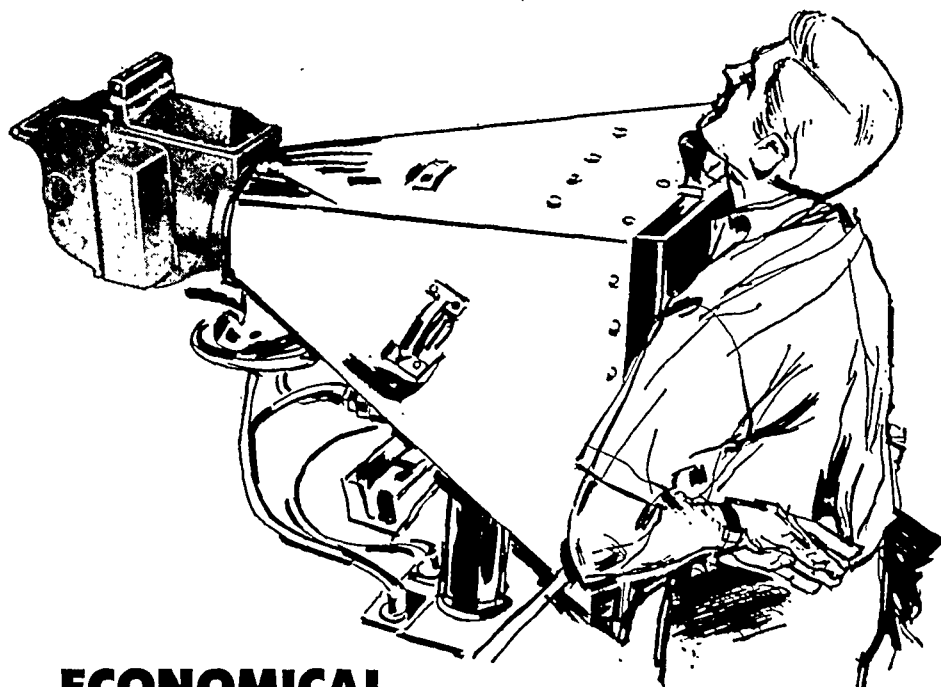
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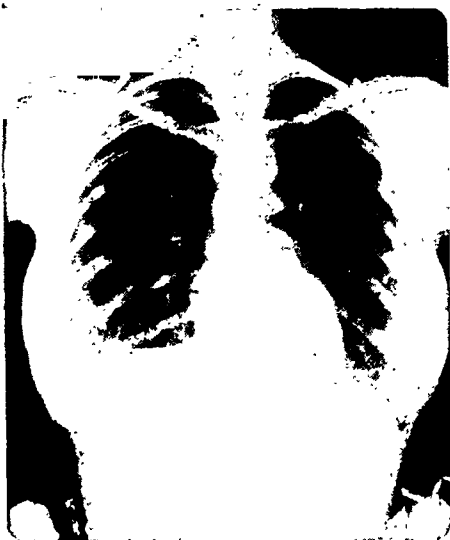
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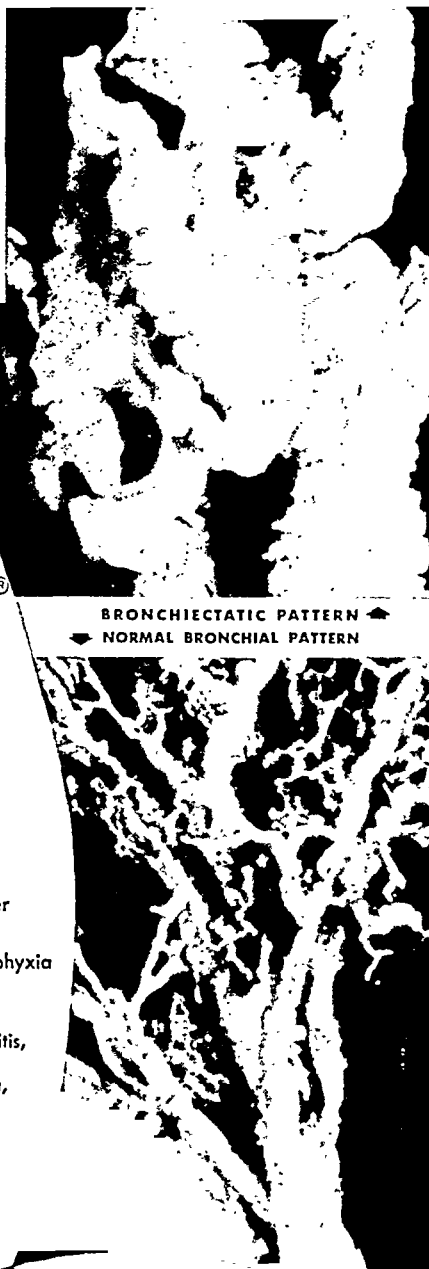
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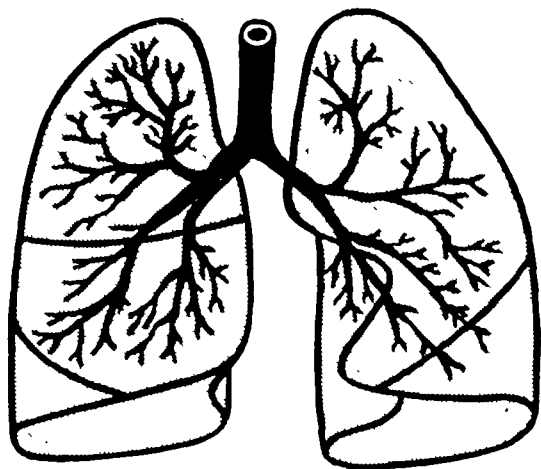


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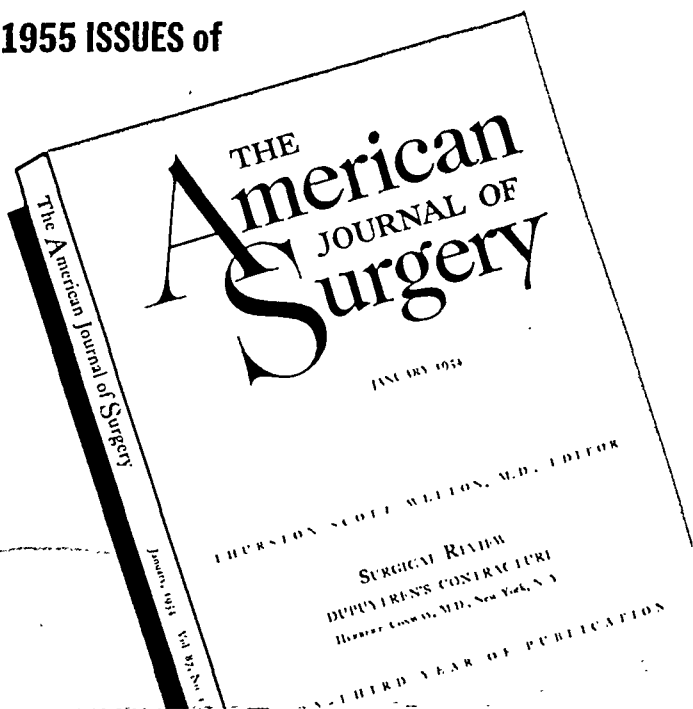
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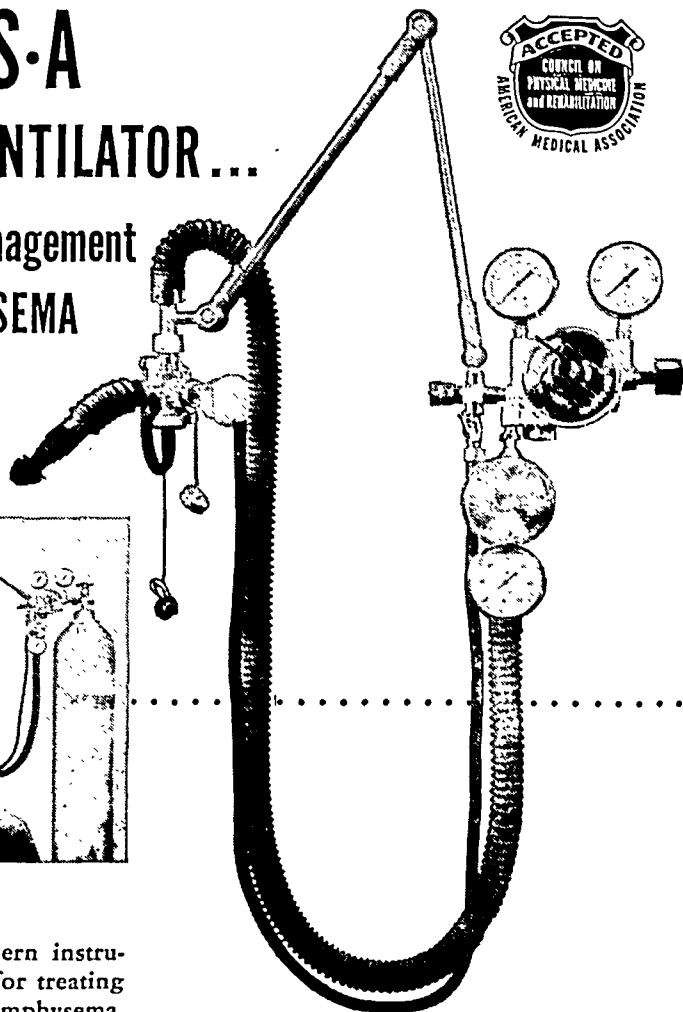
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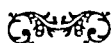
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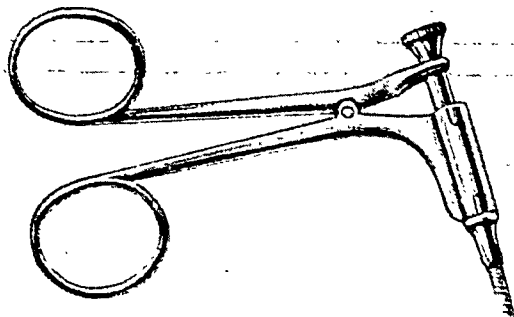
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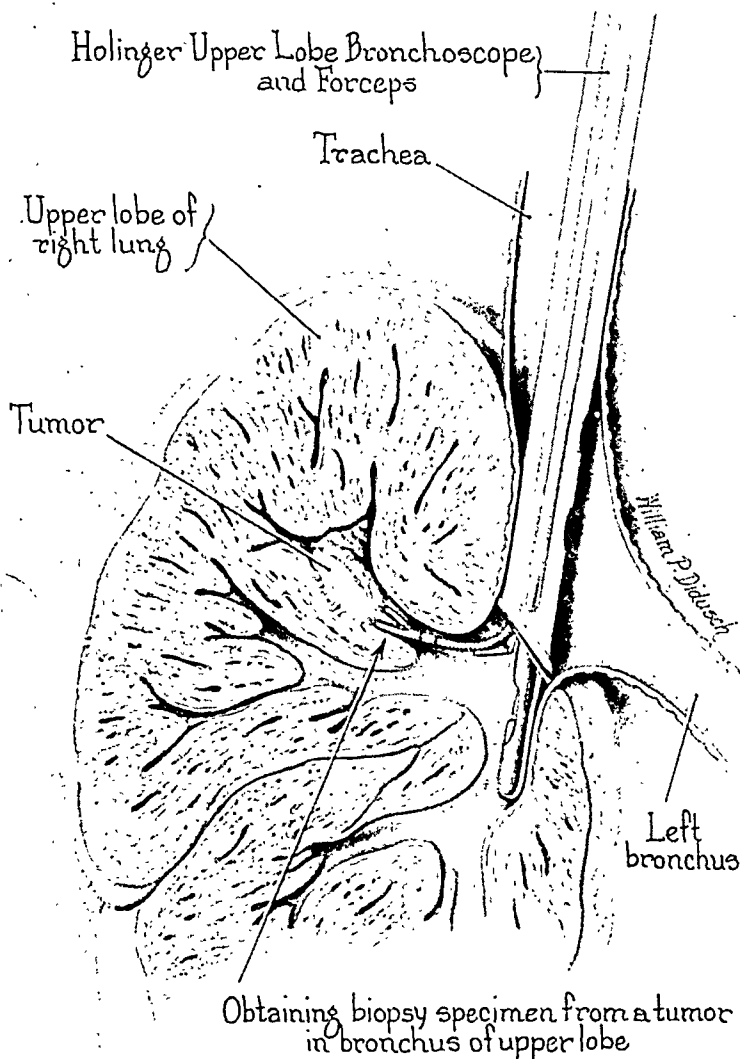
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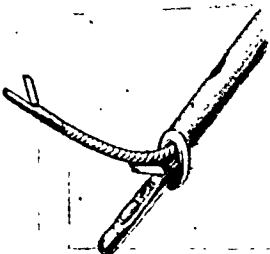


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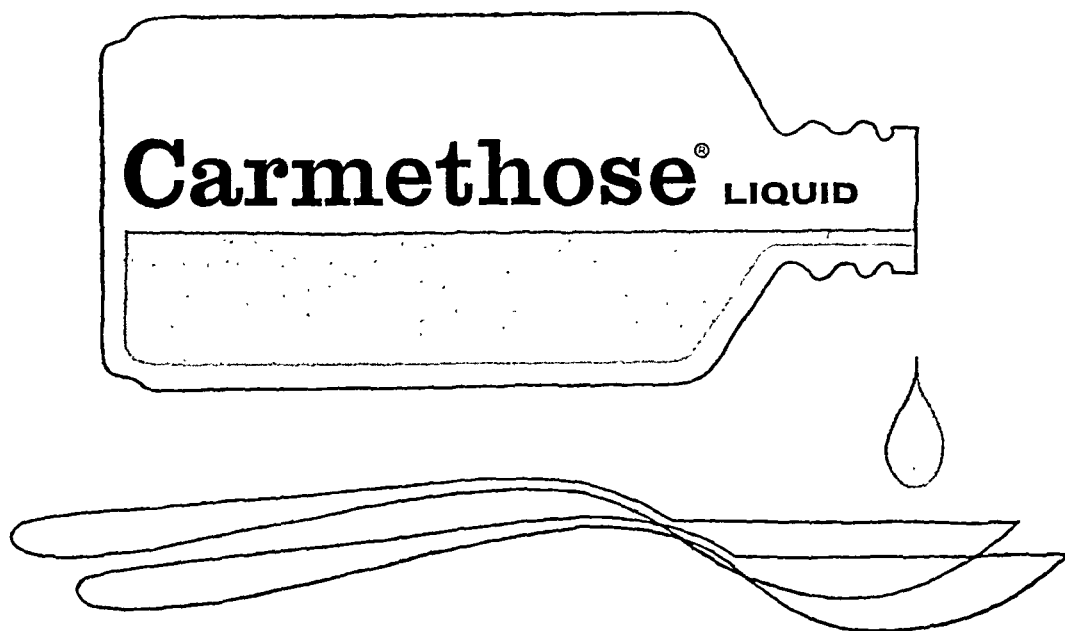
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# DISEASES *of the* CHEST

VOLUME XXVI

SEPTEMBER 1954

NUMBER 3

## Roentgenologic Changes of the Lung Associated with Isoniazid Therapy in Pulmonary Tuberculosis\*

DAVID SALKIN, M.D., F.C.C.P. and J. A. SCHWARTZ, M.D., F.C.C.P.  
San Fernando, California

The value of isoniazid as a therapeutic agent in pulmonary tuberculosis is well established but its roentgen effects have not been so well determined and need further clarification. Beneficial changes described by various authors include resorption of lesions, better definition (hardening), diminution of the extent and density of homogenous shadows, disappearance of post-hemorrhagic spreads, and decrease in size or closure of cavities or thinning of their walls.

Most of the published studies mention chiefly the general incidence of roentgen improvement and present great variation in results. For example, both the United States Public Health studies<sup>1</sup> and the Veterans Administration<sup>2</sup> report some degree of roentgen improvement in about 60 to 70 per cent of patients and moderate and marked degrees in 40 to 50 per cent. The British Medical Research Council<sup>3</sup> found moderate improvement in 20 per cent, Tanner<sup>4</sup> in 17 per cent, and Brun<sup>5</sup> and Maccone<sup>6</sup> found few noteworthy changes.

The time of appearance of the roentgen changes has been described as occurring early by some and late by others. It has also been noted that certain types of lesions respond better than do others. Good results were noted most often in fresh exudative lesions and poorest results in fibrotic lesions and old cavities.<sup>6-8</sup> The incidence of such improvement has been determined in only a small sporadic series of cases; for example, the British Research Council<sup>3</sup> reported improvement in 40 per cent of 51 cases of acute progressive disease, Witkind<sup>9</sup> found only one improvement in 12 cases of caseous pneumonia, and Collins<sup>10</sup> noted favorable changes chiefly in the exudative element of chronic cases. The improvement reported in cavities also varied markedly. Tchertkoff<sup>11</sup> reported a decrease in size in 53 per cent, with cavity closure in 30 per cent; Duggeli<sup>12</sup> reported improvement in 50 per cent; Collins<sup>10</sup> in 45 per cent of 11 cavernous cases and

\*From the Veterans Administration Hospital, San Fernando, California, and the Departments of Medicine and Infectious Diseases, School of Medicine, University of California, Los Angeles.

Read before the California Chapter of the American College of Chest Physicians, Los Angeles, May 28, 1953.

28 per cent of 18 fibroid cases; and Robitzek<sup>13</sup> in 39 per cent with closure in 14 per cent. It has also been noted that the emergence of bacterial resistance and the conversion of sputum often showed no corresponding roentgen changes. Wacker<sup>7</sup> noted favorable x-ray changes occurring after development of resistance and Tanner<sup>4</sup> described conversion of sputum even though the roentgenogram showed an increase of the disease.

The purpose of this study is to determine the incidence of roentgen improvement produced by isoniazid in the different types of infiltrations and cavities in 106 patients, the effect of certain factors, the time of occurrence of the changes, and the effect of resistance development.

### *Clinical Data*

This group of patients presented the following features at the beginning of isoniazid therapy. The average age was 49 years and fully 20 per cent were over 60. The average duration of tuberculosis prior to treatment was over nine years. Positive sputum was present in 86 at the beginning of therapy and had been present in the others some months previously. Eighteen had not had streptomycin therapy, 42 had streptomycin in varying amounts and were still sensitive to 10 mcg., 28 showed full resistance to 10 mcg. The roentgen classification of the extent of the disease included far advanced disease in 85, moderately advanced in 19, and minimal in two. The 212 individual lungs showed far advanced disease in 108 lungs, moderately advanced in 66, minimal in 22, and no disease in 16. Thoracoplasty was present in 10 patients and significant emphysema in 35. All but four were male and 96 were white.

Isoniazid was the only chemotherapeutic agent used and the *dosage* was 150 mg. daily to 73 patients, 300 mg. to 19, and a variable dose from 225 mg. to 400 mg. to 14. None was included unless he had a minimum of three months of continuous therapy. Thus, 31 had treatment for three to six months, 50 for seven to 12 months, and 25 for 12 to 15 months.

Treatment with isoniazid was begun in March 1952 and additional cases were added up to August 1952. This analysis of the results was made as of July 1953. Where the treatment was continued to this date, the period of observation coincided with the period of treatment as was the case with 69 patients; where the isoniazid was discontinued prior to this date, the observation was continued until July 1953, unless another therapeutic agent was added.

### *Mode of Evaluation*

This study does not deal primarily with the number of patients who showed roentgen benefit but with the effect of isoniazid upon the various types of lesions presented by this group. Thus, one patient may show an old fibroid cavity, productive disease, a recent exudative infiltration, and a recent exudative cavity and all may react differently to isoniazid. Such a case was regarded as having four types of lesions classified according to the pathological characteristics of the various areas of disease.

The infiltrations were designated as inactive and active. The inactive

group included moderate sized areas of fibrosis which had shown no change for months and moderate sized areas of parenchymal calcification. The *active* group was subdivided into the classical exudative and productive lesions and, because we had frequent excellent roentgenograms, and extensive serial studies with a knowledge of the age of the infiltrates, we added two more classes; an exudative-productive group between the exudative and productive and a productive-fibroid group (fibro-productive) between the productive and true fibroid. In order of age, the classification consisted of exudative, exudative-productive, productive, productive-fibroid, and fibroid lesions. The *cavities* were similarly subdivided based upon the nature and age of the cavity, its wall, and the original associated disease.

The classifications were made at the end of the observation period and designated the status of the disease existing just prior to isoniazid therapy. No case was classified on a single roentgenogram but on a thorough knowledge of each case including series of roentgenograms encompassing not only the period of treatment but for months and years prior to treatment. This classification by hindsight was intentionally adopted to enable us to classify the pathological characteristics of the lesions as accurately as possible.

Following therapy, the infiltrations were classified as worse, no change, or improved; and, if improved, whether to a mild, moderate, marked, or excellent degree. The mild degrees of improvement implied definite though small beneficial change, whereas excellent improvement meant complete or almost complete clearing. The beneficial effects upon cavities were described as decrease in size, closure, or blocking.

Those for isoniazid therapy were selected by a system of randomization adopted by the Veterans Administration and based upon the last digit of the hospital registry number. In this study, 23 were new admissions to the hospital and 83 were hospital residents who had not done well on other therapies or who were improving too slowly.

No other tuberculostatic drug was given simultaneously and existing pneumotherapy was continued unchanged. The degree of rest was also unchanged and, except for a few acutely ill who were on strict bed rest, almost all were on a modified rest program which permitted bathroom privileges. In lesions showing previous progression or quiescence the effect of isoniazid was evaluated easily, but in lesions showing some improvement prior to isoniazid, evaluation was, of course, more difficult, and great conservatism was shown in ascribing additional benefits to the drug.

### *Infiltrations*

The inactive infiltrations were unaffected roentgenologically by isoniazid. The 27 areas of fibrosis in 27 lungs, the 12 parenchymal areas of calcification, and the numerous calcifications in the lymph nodes showed no change in appearance.

The active infiltrations numbered 135 areas, with some improvement noted in 35 (25 per cent). The incidence of degree of improvement varied



with the type of lesion present (Table I), ranging from 64 per cent in exudative cases to 4 per cent in the productive-fibroid infiltrations.

*Extent* of disease had a definite bearing upon improvement. The exudative group showed 80 per cent improved in minimal cases, 70 per cent in moderately advanced, and 33 per cent in far advanced. The exudative-productive group showed 50 per cent improved in minimal, and 12 per cent in moderate cases. The productive-fibroid figures formed too small a number to analyze. In all categories, minimal cases responded best, moderately advanced somewhat less, and far advanced poorest.

TABLE I: ALL DEGREES OF IMPROVEMENT OCCURRING  
IN THE DIFFERENT TYPES OF LESIONS

	No. Areas	No. Improved	Per Cent Improved
Exudative	36	23	64
Exudative-productive	16	6	37
Productive	28	4	14
Productive-fibroid	55	2	4
TOTAL	135	35	25

The *initial time* of roentgen improvement occurred in one month to three months and only once did it occur later. Early changes after only one month were seen in 50 per cent of the exudative lesions. Improvement then continued for months, although the greatest change occurred within the first five months with a slower but steady improvement thereafter. The *degree* of improvement followed a definite pattern. Exudative areas showed a large number of excellent and marked degrees of improvement; exudative-productive cases showed fewer excellent and marked clearings; productive and productive-fibroid areas showed chiefly lower grades of improvement.

*Streptomycin* resistance proved to be a definite factor in all the groups. Cases showing organisms which were sensitive or partially resistant to 10 mcg. streptomycin gave equal results in their reactions to isoniazid and showed about four times as many improved areas as those fully resistant to 10 mcg. streptomycin.

Although the number of cases in each group is too small for detailed analysis, they all appeared similar in the presence of such concomitant factors as presence of cavity, presence of other infiltrations, and presence of isoniazid resistance. It is true that the streptomycin group of cases form a more difficult group to treat by any method, but this, in itself, did not explain the difference in results.

Two lesions in one patient tended to react similarly to isoniazid if both showed the same pathological characteristics. In a group of 10 patients showing exudative disease in both lungs, seven showed improvement bilaterally at about the same time and degree, and three presented no change on either side. New disease developed in 10 patients while under treatment. Regression of a hitherto improving lesion occurred in very few cases.

*Cavities*

There were 81 patients with 107 distinct cavities. Decrease in cavity size occurred in 25 (23 per cent), including closure of five. Their reaction according to the pathological characters is shown in Table II.

Exudative, exudative-productive, and productive-fibroid cavities showed some degree of improvement in 27, 20, and 22 per cent respectively. Only 7 per cent of the fibroid cavities showed decrease in size. Productive cavities presented a relatively high figure of 45 per cent, and, though the total

TABLE II  
IMPROVEMENT OCCURRING IN THE DIFFERENT TYPES OF CAVITIES

	No. Cavities	No. Closed	No. Smaller	Total Improved (Per Cent)
Exudative	11	1	2	27
Exudative-productive	25	1	4	20
Productive	13	1	5	45
Productive-fibroid	44	2	8	22
Fibroid	14	0	1	7
TOTAL	107	5	20	23

numbers are small, there may have been additional bronchial disease which improved, resulting in favorable mechanical changes.

Size of the cavity was not a great factor. Closed cavities averaged 3.6 cm. in diameter; the others showing a decrease in size were 5.1 cm. and the unimproved 4.5 cm. The entire group of cavities averaged 5 cm. in diameter and ranged from 3 cm. to 10 cm. The *initial* change occurred in the first three months, and half of the cavities showed some change within two months. The maximum change occurred in 50 per cent of cavities in three months, in 25 per cent more in three to six months, and in the remaining 25 per cent after six months. Sensitivity to 10 mcg. streptomycin appeared to be a factor, for improvement occurred in 28 per cent of the sensitive cases, in 21 per cent of the partially resistant (10 mcg.), and in 13 per cent of the fully resistant. The *degree* of improvement varied from closure in five cavities, a decrease of over 50 per cent in size in seven, of 25 to 50 per cent in seven, and of 10 to 25 per cent in six.

Three cavities became smaller and then returned to their former size in two to four months. Thinning of the wall occurred four times and made the cavity difficult to see; in three of these the cavity also became smaller. The causes of this change might include improvement of a bronchial infiltration resulting in aeration of the atelectatic portions of the cavity wall. Multiple cavities in the same patient tended to react similarly if they had similar pathological characteristics; this occurred in 18 of 21 cases with such multiple cavities.

*Isoniazid Resistance Studies*

Resistance studies were made at three levels; namely, 0.2, 1.0 and 5.0 mcg. per ml. of Lowenstein-Jensen medium. It was noted that the time of resistance development did not always occur in a clean linear pattern. There was often rapid development of resistance to all levels in a short time; one month the organisms showed partial resistance to 0.2 mcg. and the next month partial resistance to 1.0 and 5.0 mcg. simultaneously. Frequent overlapping of resistance levels was common, and partial resistance to 5 mcg. often occurred before full resistance to 1.0 mcg.

In general, however, partial resistance to 5 mcg. occurred in 20 per cent of patients at three months, in 60 per cent at six months, and in 70 per cent at eight months. For purposes of attempting a correlation between resistance development and roentgen changes, the following tabulation was made showing the general average range of resistance development in most of the cases (Table III). It is to be noted that full resistance to 5.0 mcg. occurs in about five to seven months.

TABLE III  
AVERAGE RANGE OF RESISTANCE DEVELOPMENT

Mcg./ml	Partial Resistance	Full Resistance
0.2	2 - 3 mos.	2 - 4 mos.
1.0	2 - 4 "	3 - 5 "
5.0	3 - 5 "	5 - 7 "

Further correlating the roentgen changes and isoniazid resistance, the following table is highly informative (Table IV).

TABLE IV: CORRELATION OF ROENTGEN IMPROVEMENT  
AND INH RESISTANCE DEVELOPMENT

Improvement	Disease	Relation to INH Resistance
Initial Improvement	Cavity . . . . 1 to 3 mos. Infiltration . . 1 to 3 mos.	Corresponds to full resistance to 0.2 mcg. or partial to 1.0 mcg.
Peak of Rapid Improvement	Cavity . . . . . 75% in 6 mos. Infiltration . . Peak at 5 mos.	Corresponds to full resistance to 5 mcg.
Continuation of Improvement	Cavity . . . . Slight Infiltration . . Continues	Cavities show little change after the development of resistance to 5 mcg. but the infiltrations continue to improve.

From the roentgen standpoint the level of significant resistance appears to be 5.0 mcg, but how important that may be remains to be determined. Once infiltrations begin to improve they tend to do so even after resistance develops, but cavities usually do not. It is possible that, in the case of infiltrations, the benefit initiated by isoniazid is continued by natural factors. In the case of cavities, the initial action on the bronchi and the

disease in the wall apparently produces conditions favorable to intrapulmonary mechanical changes (intrinsic collapse), which local factors seem to exist for only about six months in most cases.

### *Miscellaneous Features*

*Atelectasis* occurred in a lobe or major segment 18 times in 17 patients. Within three months' treatment with isoniazid, five areas showed an increased retraction, two mildly, and three moderately. One segment of an atelectatic lobe became aerated while the rest of the lobe showed further shrinkage. All the changes occurred in cases associated with productive disease, suggesting some action on diseased bronchi.

*Blocked Cavities* occurred six times prior to therapy and four blocked during therapy—no more than the usual incidence. The drug seemed to have no effect on the production of blocked cavities, or did it influence them once they formed. There were too few so-called air-filled tension cavities to evaluate properly.

The production of *sputum* was decreased in most of the patients and, in many cases, it was difficult to obtain positive bacteriological findings despite the presence of cavity and "active" infiltration. In six patients, the sputum and gastric examinations became negative and remained so, in spite of definite cavitation.

*Symptomatic* improvement was common, and several of the more common ones are shown in Table V.

TABLE V  
PER CENT IMPROVEMENT OF SEVERAL SYMPTOMS

	All Degrees	Moderate or Marked Degree	Improvement Then Reversion
General Improvement	89	70	7
Less Sputum	77	64	7
Less Cough	78	60	8
Gain in Weight	76	57	4

About 80 per cent of patients who showed some degree of improvement symptomatically maintained it despite development of resistance to 5 mcg. isoniazid. Where symptoms did revert they did so within the six months corresponding to resistance development to 5 mcg. About 95 per cent of patients showing some roentgen improvement also showed symptomatic improvement, and about 60 per cent who showed no roentgen changes had some symptomatic benefit.

### SUMMARY

1) A group of 106 patients was treated with isoniazid for a period of from three to 15 months and the roentgen effects were observed on the various types of lesions present.

2) There were 135 areas of active infiltrations divided according to their

pathological characteristics and classified as exudative, exudative-productive, productive, and productive-fibroid groups, with roentgen improvement in 65, 37, 14, and 4 per cent respectively. The greatest improvement occurred in the more recent exudative lesions, in those of minimal or moderate extent, and in the streptomycin sensitive cases. Conversely, the poorest results were obtained in the older productive and fibroid lesions, in those far advanced, and in the streptomycin resistant cases. Initial roentgen changes occurred within three months, improvement continued rapidly up to about five months and thereafter at a slower but still steady rate. Such inactive infiltrations as true fibrosis and calcification were not altered in any way.

3) The 107 cavities in 81 patients were classified similarly to the infiltrations. Some reduction in size occurred in 25 cavities (23 per cent), including five closures. The productive cavities showed some decrease in size in 45 per cent, the fibroid in 7 per cent, and the others averaged 22 per cent. Apart from the five closures, the average decrease in size was 35 per cent, and the great majority remained small. Here, too, the initial changes occurred within three months, reaching a maximum at six months for 75 per cent of the cavities. Closed cavities were smaller than the others, but those showing only a partial decrease averaged the same size as those not responding at all. Better results were obtained in those cases sensitive to streptomycin than in those resistant to it.

4) The significant point of isoniazid resistance appeared to be at 5 mcg. Both infiltrations and cavities began to show improvement and reached initial rapid peaks within six months, corresponding roughly to development of full resistance to 5 mcg. isoniazid. After this period the cavities continued to show improvement in only 25 per cent, while almost all the infiltrations continued to show further benefit. It seems that, in the case of infiltrations, the benefit initiated by isoniazid was continued by natural factors, whereas, in the case of cavities, the initial changes produced by the drug included local mechanical alterations which operated within the shorter period of six months.

5) Symptomatic improvement occurred in almost all of the patients showing roentgen improvement and in 60 per cent of those showing no x-ray change.

### CONCLUSIONS

From the roentgen standpoint, isoniazid does not cure tuberculosis. Its use is attended with varying results ranging from excellent clearing in fresh, localized exudative infiltrations to poor results in fibrocavernous lesions. It should prove to be a valuable adjunct in the comprehensive treatment of the disease.

### CONCLUSIONES

Desde el punto de vista radiológico, la isoniácida no cura la tuberculosis. Su uso corresponde a resultados variables desde la excelente limpieza en las localizaciones infiltrativas recientes, hasta los resultados deficientes en

las lesiones fibrocavernosas. Parecería ser valiosa en calidad de adyuvante en el tratamiento global de la enfermedad.

### RESUMÉ

Du point de vue radiologique, l'isoniazide ne permet pas la guérison de la tuberculose. Les résultats obtenus par son utilisation sont variables. Ils vont de l'excellent nettoyage des infiltrations exsudatives récentes et localisées aux faibles modifications des lésions fibrocavitaires. Il s'agit donc d'un adjuvant estimable dans le traitement rationnel de la maladie.

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# Peripheral Neuritis Due to Hydrazide Derivatives\*

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The antituberculous activity of isoniazid used alone or in combination with streptomycin or para-aminosalicylic acid (PAS) has been established.<sup>1</sup> One of the most favorable properties of isoniazid is the low incidence of significant toxicity resulting from its use when doses of 3 to 5 mg. per kilogram per day are administered. Some of the reactions reported include toxic psychosis, convulsions, dizziness, euphoria, increased sensitivity to sympathomimetic drugs, hyperreflexia, weakness of the legs, headache, ataxia, muscle tremors, tinnitus, disturbed vision, insomnia, drowsiness, urinary incontinence, polyuria, delay in initiation of micturition, constipation, dryness of the mouth, drug fever, variations in sexual activity, pruritis, skin rash, nausea, vomiting, exertional dyspnea and transitory edema.<sup>2</sup> Although this is a long list, toxic reactions are infrequent. The need for discontinuing the drug because of serious toxic reactions occurs in approximately 1 per cent of cases.<sup>3</sup> It is interesting to note the dominance of toxic effects referable to the nervous system.

In our studies with isoniazid, as well as other hydrazides, we have used various dosage schedules in an attempt to evaluate therapeutic efficacy, roentgenographic response, incidence of sputum conversion, development of bacterial resistance and drug toxicity.

In the course of these studies we have observed 19 patients who have developed peripheral neuritis of varying degrees of severity. Isoniazid was administered to 15. Three received 200 mg. daily; and 11 received 400 mg. daily. These doses represent 2.5 mg. to 10 mg. per kilogram per day. Eleven of the 15 received more than 5 mg. per kilogram per day. This indicates a correlation between the size of the dose and the development of neuritis.

The isoniazid used was supplied by two manufacturers. Three patients received isoniazid alone. Nine of these 15 received 1 gram of streptomycin twice a week and 12 grams of PAS daily in addition to isoniazid. One gram of streptomycin twice a week and daily isoniazid was administered to three, one of whom had received intermittent streptomycin and daily PAS for one year.

Four were given N-isonicotinoyl-N-(hydroxypivalidene) hydrazide.<sup>4</sup> In two of them 400 mg. of this compound was given daily; in one 200 mg. was administered. The third had received intermittent streptomycin and daily PAS for one year at which time 400 mg. of N-isonicotinoyl-N-(hydroxypivalidene) hydrazide per day was added. These doses correspond to 4.3 mg.

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to 11 mg. per kilogram per day. Three out of the four received over 5 mg. per kilogram per day.

Symptoms were noted as early as two weeks after the institution of therapy but in most cases appeared after the second month (Table I)

TABLE I  
ONSET OF SYMPTOMS AFTER BEGINNING HYDRAZIDE THERAPY

	2 Weeks	2 Months	6 Months	9 Months	Over 1 Year
Isoniazid	2	6	3	1	3
N-isonicotinoyl-N-(hydroxypivalidene) hydrazide	2	1		1	

indicating a lack of strict correlation between duration of treatment and the onset of neuritis. The most common complaints were numbness, tingling, burning sensation and pain in the extremities. Fourteen had hypesthesia which was most severe in the fingers and/or toes. As the distal interphalangeal joint area was reached there was a rather abrupt increase in sensory appreciation. The findings are tabulated in Table II.

TABLE II: INCIDENCE OF SYMPTOMS OF NEURITIS IN  
NINETEEN PATIENTS RECEIVING ISONIAZID THERAPY

Clinical Manifestations	Number of Patients
Diminished vibratory sense	3
Hyperesthesia (pin prick)	4
Muscle weakness	5
Hyporeflexia	5
Hyperreflexia	6
Pain	11
Hypesthesia	14
Paresthesia	15

Although the findings were bilateral and had a typical "stocking and glove" distribution, in one patient there appeared to be a mononeuritis strictly limited to the distribution of the median nerve. In six the involvement was confined to the hands or was more severe in the hands, which is unusual for most types of peripheral neuritis. No changes were noted in skin color or temperature. Discontinuance of the responsible hydrazide usually resulted in improvement.

The pathogenesis of isoniazid peripheral neuritis is not known. One possible explanation is the interference with carbohydrate oxidation in nerve cell metabolism. In the oxidation of carbohydrate, nicotinic acid plays an important role as an essential constituent of co-enzyme I and II. One of the many reactions in which co-enzyme I participates is the conversion of pyruvic acid to lactic acid. It is possible that isoniazid with its similar structure might compete with nicotinic acid in this oxidative process thus producing a blocking mechanism. However, there was no



significant elevation of pyruvic acid levels in our patients.<sup>5</sup> Nicotinic acid also plays a role in the Krebs Cycle as co-enzyme activator for alpha-ketoglutarate dehydrogenase. Measures will be taken to determine if there is any increase in the alpha-ketoglutarate acids.

Although none of the patients showed any of the classical manifestations of nicotinic acid deficiency, the theoretical possibility exists that nicotinic acid may be useful in the management of isoniazid peripheral neuritis. It is our intention to use large doses of nicotinic acid in the patients who do not respond satisfactorily to the withdrawal of isoniazid.

### *Case Report*

B. F., a 22-year-old colored female was admitted to this hospital on March 23, 1953, with a history of anorexia, weakness, and productive cough of several weeks' duration. X-ray film revealed evidence of extensive pulmonary disease. The sputum showed tubercle bacilli. Streptomycin, PAS and isoniazid were started on March 23, 1953. By April 20, 1953, there was obvious clinical and roentgenographic improvement. Two weeks after treatment was started, she complained of numbness and pain in both hands. The pain rapidly became worse and she described this "as if my flesh were coming off." Neurological examination revealed paresthesias of the hands, hyperactive reflexes, and greatly diminished pin-point sensation of both hands. Vibratory sense and position sense were intact. Gradually there was voluntary limitation of movement of both hands and fingers. Three weeks after the onset of symptoms there was considerable atrophy of the intrinsic muscles of the hands, particularly the thenar eminences, with almost complete loss of movement. On June 30, 1953, isoniazid was stopped. The peripheral neuritis continued for another month and then gradually subsided.

### SUMMARY

Peripheral neuritis following isoniazid has been observed in 19 patients. The chief components are paresthesias of both upper and lower extremities. There was no strict correlation between duration of therapy and onset and severity of symptoms. In most instances symptoms gradually subsided following cessation of the drug.

### RESUMEN

Se ha observado neuritis periférica en 19 enfermos después del uso de la isoniácida. Los principales síntomas son parestesias en ambas extremidades inferiores. No hay estricta correlación entre la duración del tratamiento y el principio y la severidad de los síntomas. En la mayoría de los casos los síntomas ceden después de la suspensión de la droga.

### RESUME

Des études du système nerveux périphérique ont été faites après un traitement à l'isoniazide chez 19 malades. Les éléments essentiels des troubles sont des paresthésies des extrémités. On ne peut noter de rapport net entre la gravité des manifestations et la longueur du traitement. Dans la plupart des cas, les signes pathologiques s'atténuaient progressivement après qu'on eût cessé l'utilisation du produit.

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# Results of the Use of Hydrazide of Isonicotinic Acid in the Therapy of Pulmonary Tuberculosis, Tuberculous Meningitis and Empyemas\*

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## PULMONARY TUBERCULOSIS

*Material:* Number of patients: 144. Type of disease: productive—exudative, mostly cavitary. Form: chronic. Daily dosage of INH: 4-10 mg./Kg. Duration of treatment: three to six months.

### *Results:*

#### Clinically:

Pronounced improvement in 6 cases

Great improvement in 54 cases

Little improvement in 63 cases

No improvement in 19 cases

Deterioration in 2 cases

} Death in 6 cases

#### X-ray Changes:

Great improvement in 14 cases (in 6 cases disappearance of cavities)

Little improvement in 46 cases

No change in 82 cases

Deterioration in 2 cases

#### Sputum Bacteriology:

123 patients had positive sputum for acid fast bacilli. In 41 the sputum was converted to negative. In 82 the sputum remained positive, and in 21 who had negative sputum, it remained negative.

#### Relapse:

After initial improvement 16 patients relapsed five months after beginning of treatment despite uninterrupted therapy.

#### Generally:

Favorable effect on the symptoms of the disease in high percentage; on the focal process moderate effect and in small percentage.

## TUBERCULOUS MENINGITIS

- 1) Simple tuberculous meningitis treated by oral administration of hydrazide of isonicotinic acid alone.

Number of patients: 10.

#### Daily Dosage:

5- 10 mg./Kg. in two cases

10 mg./Kg. in eight cases

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**Total Dosage:**

- 40- 60 Gm. in four cases
- 60-100 Gm. in three cases
- 100-150 Gm. in three cases

**Results:**

Great clinical improvement without morbid signs and symptoms in two cases. Complete clinical and laboratory recovery in eight cases. With duration of this favorable obtained result:

- from two months in one case; three months in five cases;
- four to five months in two cases.

Insufficient control time of stability and duration of the above mentioned eight cases.

2) Simple tuberculous meningitis previously treated with streptomycin and PAS without benefit and later treated with INH.

Number of patients: 15.

Total amount of streptomycin given intramuscularly from 70 to 220 Gm.; intraspinaly 4.5 to 11 Gm.

Total amount of PAS: in eight cases from 600 to 2,200 Gm. intravenously.

**Daily dosage of INH:**

- from 5-10 mg./Kg. in 10 cases
- 5 mg./Kg. in five cases

**Total dose of INH:**

- from 35-50 Gm. in three cases
- 50-70 Gm. in six cases
- 70-95 Gm. in six cases

**Results:**

In one case, death. In six cases only clinical recovery with abnormal spinal fluid findings. In eight cases complete clinical and laboratory recovery.

**Duration of clinical and laboratory recovery:**

- In one case, two months; one case, three months; one case, four months; one case, five months; four cases, six months.

3) Meningitis associated with pulmonary tuberculosis.

Number of patients: 23. Treated previously with streptomycin from 50 to 270 Gm. intramuscularly and 3 to 11 Gm. intrathecally, and PAS intravenously (in eight cases) from 400 to 2,200 Gm. Patients have failed to respond to this form of therapy and so INH treatment was started.

**Daily dosage of INH:**

- 5-10 mg./Kg. in 20 cases
- 10 mg./Kg. in three cases

**Total dose of INH:**

- 25-130 Gm. orally

**Results:**

- Death in two cases

Deterioration in one case

No change in three cases

Improvement in six cases

Clinical and laboratory recovery in 11 cases

Duration of recovery:

Two months in two cases; three months in three cases; four months in two cases; five months in one case; six months in three cases.

On a total number of 48 patients of above three groups the following results were obtained:

Death in three cases

Deterioration in one case

No change in three cases

Improvement in 14 cases

Complete clinical and laboratory recovery in 27 cases.

### EMPHYEMATA

Number of cases: 18.

Treated previously by repeated aspiration and intrapleural administration of streptomycin and PAS and solution of hydrazide of isonicotinic acid unsuccessfully.

In 11 cases of tuberculous empyemas without bronchopleural fistulae, occurring as a complication of artificial pneumothorax, INH was given orally in daily dosage of 5 mg./Kg. for two to four months.

*Results:* Absorption of pleural effusion in all cases; in five cases enabling the pneumothorax to be continued. In six cases complete re-expansion of the collapsed lung with pleural obliteration was achieved.

In seven cases of tuberculous empyema with bronchopleural fistulae, in three as a result of artificial pneumothorax and in four as a complication of spontaneous pneumothorax, drainage was carried out.

INH therapy was instituted 10 mg./Kg. daily for five to eight months.

*Results:* Complete absorption of purulent effusion in four with re-expansion of the collapsed lung. Diminution of exudation in three. Closure of chest sinuses, healing of chest wall infection.

### *Observations and Conclusions*

1) As regards the toxicity administration of daily dose of 10 mg./Kg. for months has not provoked undesirable side effects except some slight psychic disturbances. For example, a man, aged 38, suffering from meningitis and treated with hydrazide of isonicotinic acid and presenting great improvement tried to commit suicide by taking 80 tablets of INH (50 mg. per tablet). One hour later he vomited so that part of the tablets were expelled. Besides the acute toxic symptoms he presented hemiplegia which is improving, with residual paresia and a marked state of euphoria. A woman aged 27, suffering from pulmonary tuberculosis and treated with streptomycin, PAS and INH took by mistake 24 tablets of INH (50 mg. per tablet) daily for five days with resulting intense dizziness, headache and somnolence; after discontinuance of administration of the drug for three

days the symptoms disappeared to reappear again after a new course of 18 tablets daily for four days. Cessation of treatment: disappearance of toxic symptoms. Despite having taken in a period of 12 days, 192 tablets = 9 Gm. and 600 mg. of INH, toxic symptoms were observed but were transient without any sequelae.

2) Effect on pulmonary tuberculosis. Favorable effect on toxic symptoms was noted. The more acute and intense the morbid manifestations the greater the favorable effect. The milder the morbid manifestations the lesser the favorable effect. The more recent the focal process the greater the favorable effect. The older the focal process the lesser the favorable effect. In a small percentage of cases pronounced favorable results were observed. In a high percentage, life of patients was prolonged without morbid symptoms but without change in the focal process.

3) Effect on tuberculous meningitis, selective favorable influence with high percentage of complete clinical and laboratory recovery (27 out of 48 cases) was recorded. This selectivity is explained by the fact that the orally administered INH has a great penetrating and diffusion power in a high concentration rate in the spinal fluid as was determined by the researches of Bunger, Lass, Muller (*Deut. Med. Wochenschrift*, 19.IX.52, No. 38). In addition no hydrocephalus was observed in our cases owing to the fact that INH is administered orally and not intrathecally whereas the administration of streptomycin intraspinally favors the appearance of hydrocephalus, which aggravates the course and prognosis of meningitis as the necropsy researches of Zollinger,<sup>1</sup> Schwartz,<sup>2</sup> and Eleutheriou<sup>3</sup> have proved.

4) Selective favorable effect was noted with healing of tuberculous empyemas and of fistulae of empyemas by oral use of hydrazide of isonicotinic acid and not by local application of the drug. However, repeated aspiration and evacuation of effusion should be carried out during treatment.

The administration of larger daily dosage of INH is indicated as 10 mg./Kg. and not the initial proposed dose of 4 to 5 mg./Kg. As regards to the duration of administration of this agent we obtained favorable results by administration of this drug up to six months.

Further investigations are needed in order to solve the problem of the drug resistant strains. The published report of the British Medical Council of scientific researches (*Brit. Med. Journal*, X, 1952) mentions that by use of hydrazide of isonicotinic acid Koch bacilli show a resistance in 11 per cent at the end of the first month, 52 per cent at the end of the second month, and 71 per cent at the end of the third month.

Another question is the possibility of a synergistic action of hydrazide of isonicotinic acid with some other therapeutic agents such as streptomycin and PAS in order to obtain on the one hand more favorable results and on the other hand to decrease and delay the emergence of bacillary resistance to the combined administered drugs.

We consider INH a drug of attack so that by achievement of favorable

clinical results we may continue later with the combined treatment of streptomycin and PAS.

### SUMMARY

The hydrazide of isonicotinic acid was administered to 144 persons with pulmonary tuberculosis, 48 with meningitis and 18 with empyema.

In doses of 10 milligrams per kilo of body weight, the only undesirable side effect were slight psychic disturbances.

Favorable effects were observed on toxic symptoms of pulmonary tuberculosis and in a large percentage, life was prolonged, but no change was observed in the lesions themselves.

Complete clinical and laboratory recovery occurred in 27 of the 48 cases of meningitis.

Selective favorable effect was noted with healing of tuberculous empyema and of fistulae by oral use of the drug.

### RESUMEN

Se administró la hidracida del ácido isonicotínico a 144 personas con tuberculosis pulmonar (48 con meningitis y 18 con empiema).

A la dosis de 10 miligramos por kilo de peso, los únicos efectos indeseables parecen ser ligeros trastornos intestinales.

Se observaron efectos favorables sobre los síntomas tóxicos de la tuberculosis pulmonar y en gran porcentaje, la vida se prolongó, pero no se observó cambio en las lesiones mismas.

Se obtuvo una completa recuperación clínica y según el laboratorio de 27 entre 48 casos de meningitis.

Se notó efecto selectivo en la curación del empiema tuberculoso y de las fístulas mediante la administración oral de la droga.

### RESUME

144 personnes atteintes de tuberculose pulmonaire (48 cas avec méningite et 18 cas avec pleurésie purulent) ont subi un traitement par l'isoniazide.

En utilisant les doses de 10 mmgr. par kilogramme de poids corporel, les seuls inconvénients furent de légers troubles.

On observa des effets heureux sur les signes d'intoxication de la tuberculose pulmonaire, et dans un nombre important de cas, il y eut une prolongation de la durée de la vie. Mais l'auteur ne constata pas de modifications des lésions elles-mêmes.

Une guérison complète clinique et biologique, survint dans 27 des 48 cas de méningite.

On constata quelques effets favorables sur les pleurésies purulentes et sur les fistules en utilisant le produit par voie buccale.

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# Management of Spontaneous Pneumothorax\*

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Spontaneous pneumothorax occurring in the apparently healthy individual was first named and described by Itard<sup>1</sup> in 1803. In 1826 Laennec<sup>2</sup> accurately described the occurrence of such a phenomenon, and following McDowell<sup>3</sup> in 1856, who described the condition in a tuberculous patient, the etiology was accepted as tuberculous in the majority of cases until Kjaergaard<sup>4</sup> (1932 and 1933) revealed that patients with spontaneous pneumothorax had no more tuberculosis than could be found in the general population. Leggett et al<sup>5</sup> (1934) found negative Mantoux tests in 50 per cent of their cases. Evidence of this basic pathological fact was furthered by Blackford<sup>6</sup> in 1939.

In a review of the literature on this subject, the monumental work by Kjaergaard,<sup>4</sup> the experimental work by Macklin,<sup>7,8</sup> and the clinical observations of Hamman<sup>9</sup> are easily outstanding. To those interested in the history of our knowledge of this subject from the earliest times up to 1903, we suggest the study of Emerson's monograph.<sup>10</sup>

Many names have been suggested and used to describe the non-tuberculous, non-traumatic pneumothorax in apparently healthy individuals. Spontaneous pneumothorax is by far the most commonly used; yet it infers that this type of pneumothorax occurs without known cause. From the work of the above,<sup>4,7-9</sup> as well as the operative findings and autopsy reports of others,<sup>11-17</sup> the etiology and pathogenesis is now well established, and perhaps a more descriptive term might be devised. None of the terms as listed in the literature are based on etiology or pathogenesis. Any terms which we have tried to devise that would have such a basis are quite clumsy, and we suggest return to the term first suggested by Kjaergaard<sup>4</sup> in 1933, to wit: "Pneumothorax simplex."

In the period 1949 to 1952 we have observed and treated 114 patients with spontaneous pneumothorax. Cases due to tuberculosis or other disease or trauma of any type, accidental or surgical, have been excluded from this series.

## *Source of Material*

This material came from Medical and Surgical Chest Conferences at Brooke Army Hospital, Fort Sam Houston, Texas, from the Thoracic Surgery Center, Randolph Air Force Base, Texas, and from private cases.

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*Age*

The average age was 27.5 years. The youngest was a newborn infant, two months premature, and the oldest was 73 years. Fifty per cent of the total cases were under 25 years of age, and 80 per cent were under 30 years of age.

*Sex*

Male .....	104 patients
Female.....	10 "
TOTAL.....	114

*Types of Spontaneous Pneumothorax*

Pneumothorax—First attack .....	61
Pneumothorax—Recurrent attacks .....	47
Hemopneumothorax .....	6
TOTAL PATIENTS .....	114

Early in the first part of the series (1949), bronchoscopy and bronchography was done in 25 consecutive cases of initial attacks after expansion of the lungs. There were no positive findings on bronchoscopy, and the bronchograms were all negative. This procedure was then discontinued as a routine practice, being done thereafter only as indicated by symptoms or appearance of the lung after expansion.

*Treatment of Unilateral Spontaneous Pneumothorax—First Attack*

Bed rest only .....	10
Thoracentesis only .....	12
Intercostal catheter decompression .....	12
Thoracoscopy with catheter decompression .....	12
Thoracoscopy with instillation of glucose and catheter decompression .....	8
Thoracoscopy with insufflation of talc and catheter decompression .....	5
Thoracotomy with removal of large bullae and poudrage.....	1
Decortication .....	1
TOTAL PATIENTS .....	61

In 10 of the 61 patients, the degree of pneumothorax was quite small and no treatment was given but bed rest. We felt that the pneumothorax was so small that thoracentesis or insertion of an intercostal catheter might be injurious. In 12 cases thoracentesis alone (for the removal of air) was done. In the total 22 cases treated by bed rest only or bed rest and thoracentesis, there are four known recurrences.

In 12 cases treatment consisted of insertion of an intercostal catheter into the pleural space and decompression through a water trap. In 12 cases the catheter decompression was preceded by thoracoscopy. In these 24 cases there have been two known recurrences.

In eight cases thoracoscopy had been followed by instillation of 50 cc. of 50 per cent glucose into the pleural cavity, followed by catheter decompression. There has been one known recurrence.

In five cases during thoracoscopy talc (talcum powder, U.S.P.) was insufflated. There are no known recurrences.

In a total of 37 cases the intercostal catheter decompression was used. In the 22 cases treated by bed rest alone or bed rest and thoracentesis, an average of three weeks was required for complete expansion. The shortest time was eight days and the longest six weeks. Of the 37 in which intercostal catheter decompression was used, 33 were expanded within a few minutes following catheter insertion. Two of the remaining four were expanded by the second day, and the remaining two required six and eight days, respectively.

In one case, even though it was the first attack, the presence of a large bulla evident in the collapsed lung by roentgenogram led us primarily to a thoracotomy with removal of the bulla and poudrage. There has been no recurrence in this case.

In the last case in this group, an unexpanded lung developed as a sterile fibrothorax from the initial spontaneous pneumothorax. This patient had received elsewhere treatment in the following order: Bed rest for two weeks, repeated thoracenteses for three weeks, catheter decompression for two weeks. It is of interest to note that active treatment (thoracentesis) was delayed for two weeks, and continuous active treatment (intercostal catheter decompression) was delayed for five weeks. Decortication was necessary. There has been no recurrence.

In the early part of the series (1949), thoracoscopy was done in 25 cases (Curti and Poulsen<sup>18</sup>). In only two instances were blebs noted that could not be demonstrated on roentgenogram. For that reason it was discontinued as relatively useless. In the instances where thoracoscopy was done, a catheter was installed for decompression in all cases and instillation of glucose (eight cases) or insufflation of talc (five cases) was done. There were no complications or recurrences from the talc or glucose treated cases. The use of 50 cc. of 50 per cent glucose was discontinued because of pain. Intravenous procaine drip, intravenous morphine, and even the mixture of pontocaine with the glucose failed to reduce the pain to a reasonable degree. Pain was severe in six cases and moderately severe in two. The pain did not abate until an average of 72 hours had elapsed. Insufflation of talc was discontinued for the reason that it was difficult through the thoracoscopy trocars to place the talc exactly where desired. Too frequently it got into the interlobar fissures, mediastinal surface of the lobes, and the diaphragmatic surface of the lower lobe. These places, we feel, are undesirable in the use of talc.

*Recurrent Spontaneous and Chronic Pneumothorax*

Unilateral	28
Unilateral chronic unexpanded lung	6
Bilateral: Alternating	11
Bilateral: Simultaneous	2

TOTAL PATIENTS

*Treatment of 34 Unilateral Recurrent and Chronic  
Spontaneous Pneumothoraces*

Thoracotomy with resection of blebs, poudrage, and catheter decompression.....	18
Decortication with removal of blebs and catheter decompression .....	6
Catheter decompression .....	4
Thoracoscopy with instillation of glucose and catheter decompression .....	2
Phrenic emphraxis .....	1
Refused treatment .....	3
TOTAL PATIENTS .....	34

In the 18 cases operated, blebs or bullae were found in all but one. They were removed by excision, suturing the base, and inversion of this line of sutures by a secondary line of sutures. Poudrage was done by talc followed by catheter decompression. In the last four cases the pleura was also rubbed by gauze (Churchill<sup>19</sup>) previous to dusting by the talc. In the case wherein blebs were not found, rubbing and dusting with talc alone was done.

In the six cases of unexpanded chronic pneumothorax, it is of interest to note that four of the six developed the condition on their first recurrence. All required decortication of the thick fibroplastic peel. In all but one, upon expansion of the lung blebs or bullae were noted which were removed.

The four cases of catheter decompression, one of phrenic emphraxis, and two of instillation of glucose were all done in patients with marked bilateral emphysema, heart disease, considerable age, or a combination of all three.

There have been no recurrences in the 24 cases subjected to thoracotomy. One of the four treated by catheter decompression had a recurrence six months later, and two of the three refusing treatment had recurrences within the year.

*Bilateral Spontaneous Pneumothorax*

There were 11 alternating and two simultaneous cases. None was of the progressive tension variety, and in only one was there severe dyspnea on admission. The term "alternating pneumothorax" is used in this series only where the contralateral lung had collapsed at least two months after the original side was completely expanded.

In eight of the 11 alternating pneumothoraces, thoracotomy was done on the side of the last attack. Blebs were found in all cases operated. These were removed, followed by poudrage and catheter decompression. There was only one recurrence, and this occurred three months later on the contralateral side. In one case the pneumothorax was treated by aspiration, one by glucose instillation and catheter decompression following thoracoscopy, and one by bed rest alone. There was no recurrence in these three cases. The one treated by bed rest required three months for expansion (refused treatment), and the one treated by thoracentesis took three and one-half weeks, whereas the eight operated were expanded at

the completion of operation and remained so, and the one treated by catheter decompression was expanded in a few minutes on one side, and on readmission four months later was expanded on the contralateral side in one day.

In the instance of the two simultaneous pneumothoraces, one was treated by bilateral simultaneous catheter decompression, one lung expanding in a few minutes and the other in two days. In the second case, immediate bilateral expansion occurred following catheter decompression and bilateral thoracotomy at four month intervals was done. Blebs were found on both sides. These were removed, poudrage done, and catheter drainage established.

### *Spontaneous Hemopneumothorax*

The onset in four of the six cases was sudden, and all four were in varying degrees of shock when first seen. In the six cases, treatment consisted of multiple thoracenteses, and amounts of blood of 400 to 4,100 cc. were removed by thoracenteses over a period averaging five days. One of us (C.G.) suggested the use of hematocrit in testing samples of blood withdrawn at each thoracentesis in order to determine whether bleeding was continuing, of intermittent character, or had cleared. This ingenious idea has been used and found eminently satisfactory. It is also, we might add, of considerable value in attempting to make the diagnosis of continuing intrathoracic bleeding in trauma to the chest. No operative interference or catheter decompression was used in five cases. All were expanded by the end of two weeks. In the sixth case, expansion of the lung was impeded by a fibroplastic residual and this was decorticated. In two of the cases spontaneous hemopneumothorax occurred in alternating spontaneous pneumothoraces. In one case the hemopneumothorax occurred on the right, and later left spontaneous pneumothorax occurred. In the second case spontaneous pneumothorax occurred on the right, and later hemopneumothorax on the left.

### *Summary of Treatment of All Cases*

Bed rest only	11
Thoracentesis only	18
Intercostal catheter decompression	17
Thoracoscopy with catheter decompression	12
Thoracoscopy with instillation of glucose and catheter decompression	11
Thoracoscopy with insufflation of talc and catheter decompression	5
Thoracotomy with removal of blebs and bullae, poudrage, and catheter decompression	28
Decortication	8
Phrenic emphysexis	1
Refused treatment	3
TOTAL PATIENTS	114

### *Discussion*

*Incidence.* The incidence of unilateral spontaneous pneumothorax is far more than detailed in the literature. There must be numerous cases never

diagnosed, as the symptoms may be mild or absent and the case is therefore missed unless a roentgenogram is taken. Ten per cent of our cases had no symptoms, being found on routine chest films. In situations where roentgenograms are taken routinely or for even mild symptoms (Armed Forces hospitals), the number found is considerably more than in civilian practice. In the U. S. Army<sup>20</sup> 873 cases were reported as hospitalized in 1943. In 15 per cent it was found necessary to separate them from the Service because they were deemed sufficiently disabled.

*Side involved.* In our series the cases were equally divided as to right and left sides. Charr<sup>21</sup> reports more on the left side and credits this to more pulmonary motion due to cardiac action. This explanation is difficult to accept, as physical activity with obvious increase in ventilatory function seems not to be a factor. Leach<sup>22</sup> reports 38.8 per cent as having no physical activity, and mild or unstated activity in 50.4 per cent of 129 cases. In our series 20 per cent occurred in bed while resting alone, and in 30 per cent more there was only mild physical activity.

*Recurrence rate.* There were 47 cases of recurring spontaneous pneumothorax in our series, and when one adds the 11 bilateral and the 11 recurrences after treatment or refusal of treatment, the total is 69 recurrences out of 114 cases (60.5 per cent). The recurrence rate as reported is from 5 to 45 per cent.<sup>4,23-27</sup>

*Etiology.* There are many<sup>4,7-10,12,13,28-39</sup> excellent dissertations on etiology. Only a brief review of the experimental work and clinical substantiation is in order here, for it forms the basis of our ideas concerning, first, the active treatment of the first attack, and second, surgical intervention in recurrent cases. Kjaergaard<sup>4</sup> felt that spontaneous pneumothoraces were due to the rupture of subpleural vesicles of two types—one, a vesicle developing in the apex adjacent to old tuberculosis, and second, emphysematous vesicles occurring on the basis of localized emphysema without scar tissue. As the majority of vesicles and blebs are found in the apices, the observation of Ornstein and Lercher<sup>26</sup> concerning disproportionate overventilation of lung apices during a Valsalva maneuver may well explain the anatomical location. Macklin<sup>7,8</sup> pointed out on both experimental and clinical evidence that first there was atelectasis or some form of partial bronchial obstruction giving local obstructive emphysema with resultant break in the alveoli, permitting air to enter the pulmonary paravascular tissue. From the interstitial emphysema air traveled up and into the mediastinum. The mediastinal emphysema could then break into one or both pleural cavities and/or go up into the neck or even travel retroperitoneally. He also produced pneumothorax from experimentally produced mediastinal emphysema. One of us (L.M.S.) has seen cases of large bleb formation in certain pneumonias of childhood, and spontaneous pneumothorax in cases of severe dyspnea in bronchial foreign bodies and in "bull-neck" diphtheria, all of these being evidences and results of obstructive emphysema. Hamman<sup>9</sup> furthered this contention in pointing out the clinical relationship between mediastinal emphysema and spontaneous pneumothorax. These contentions of Kjaergaard, Macklin, and Hamman

have many supporting clinical reports.<sup>28-30,31-36,40</sup> Hamman<sup>9</sup> reported that two cases out of 27 spontaneous pneumothoraces had mediastinal emphysema. Dickie<sup>33</sup> reported that in 20 patients, six had pneumothorax alone, seven pneumo-mediastinum, and seven had both.

Draper<sup>28</sup> points out that although spontaneous mediastinal emphysema and spontaneous pneumothorax may occur together, the vast majority of pneumothoraces occur without *demonstrable* mediastinal emphysema. We concur in this, for in our 114 cases, we did not see mediastinal emphysema in any, and in only one case could Hamman's sign<sup>9</sup> be heard. This patient was a physician in whom the crackling noise synchronous with the heart-beat was audible without a stethoscope; yet the mediastinal emphysema was not detected by roentgenograms. Wise<sup>36</sup> makes, we feel, an important point in stating that in many cases of spontaneous pneumothorax in which mediastinal emphysema was not recognized previously, the symptoms are severe and similar to those with spontaneous pneumothorax. Perhaps when cases require differential diagnosis between coronary occlusion, dissecting aneurysm, ruptured peptic ulcer (Hamman<sup>9</sup> and Miller<sup>34</sup>), and spontaneous pneumothorax, and if no air is seen in the pleural cavity, the precordium should be *carefully* and *repeatedly* auscultated and a search for roentgenographic evidence of mediastinal emphysema should be done *repeatedly*.

The facts and theories as substantiated by clinical and experimental evidence are not, as at first glance, contradictory, for whether there is an escape of air directly from the "valvesicle" (Kjaergaard) into the pleural cavity, or from the mediastinum (Macklin), both require certain changes in the lung parenchyma (localized obstructive pulmonary emphysema—Macklin, or localized emphysema on the basis of scar tissue—Kjaergaard). It may be presumptuous to interpret other men's experimental work, but on the basis of our clinical experience it might not be unreasonable to assume that these two are different phases of the same or similar processes, Macklin's being more of the acute type, whereas Kjaergaard's statements as to pathogenesis obviously refer to lesions that require time to evolve. Perhaps the vesicle or bleb may result quickly, but the "scar" of the lung parenchyma requires time.

### *Methods and Basis of Treatment*

In general, we feel that whether the source of air leaking into the pleural cavity is directly from the vesicle or bleb, or indirectly from such sources via the mediastinum, the problem is one of overcoming the effects on the lungs. If the leak is directly from the vesicle or bleb, it is obvious from the results that sudden expansion of the immediate adjacent normal, but collapsed, lung stops the leak. If we consider the indirect route (interstitial emphysema and mediastinal emphysema) being treated by immediate expansion, we have an even better basis for such treatment. This route requires the presence of partial atelectasis of at least a segmental or sub-segmental degree. Under such circumstances, leaking of air into the pulmonary parenchyma from the emphysematous area distal to the partial atelectasis would certainly continue or tend to be prolonged, as the factor

of air drift could not be effective. There could be no air drift across a segmental plane if the segments adjacent to the one containing the partial atelectasis are collapsed as part of the pneumothorax.

It is often difficult to visualize bullae by roentgenogram and only rarely can one see vesicles or blebs. Sycamore<sup>41</sup> demonstrated the fact that bullae can be seen after reexpansion of the lung. Kjaergaard,<sup>4</sup> Gordon,<sup>42</sup> and Castex and Mazzei<sup>43</sup> have discussed this problem. The difficulty of visualizing any abnormality by roentgenogram with exception of the pneumothorax is commonly encountered. Bullae and blebs have in our experience been most evident when the lung was collapsed or in the process of expansion. The absence of such findings on roentgenogram does not constitute contraindication for surgery, for in the combination of our series and those of Brock,<sup>15</sup> Meade and Blades,<sup>16</sup> Brewer, Dolley and Evans,<sup>12</sup> and Haver and Claggett,<sup>17</sup> 91 per cent had blebs, bullae, cysts, etc., found at operation.

*Spontaneous pneumothorax—Initial attack.* Considering the relative greater speed and expansion of the greater percentage of such cases by intercostal catheter decompression, as compared to bed rest alone or bed rest and intermittent thoracenteses, we can find no reason for not interfering where possible as promptly as possible. The expansion of the greatest majority of cases in from a few minutes to two days, as compared to an average of three weeks, is important from an economic standpoint. In these days of not only a shortage of hospital beds, but also high cost of hospitalization and economic loss to the patient hospitalized for long periods, this time differential should be of great significance.

The natural reluctance to put a foreign body (i.e., catheter) into the pleural cavity in a type of case in which the majority will *eventually* resolve themselves is understandable, but we would like to point out that in the 37 cases in which intercostal catheters were installed by 11 different operators, there were no complications (no infections and no residual complications). Considering the absence of complications, the ease and rapidity of treatment, and the relative lessened economic cost, we feel this is by far the choice of treatment. In addition to these factors, the obvious advantage of immediately reducing or eliminating pleural complications of infection and/or unexpanding lung is of value even in the few cases in which these complications occur following the initial attack.

The routine of our use of intercostal catheter decompression is approximately as follows: As soon as there is roentgenographic evidence of spontaneous pneumothorax, an intercostal catheter varying from 16 to 20 French is inserted via trocar under local anesthesia in the second interspace anteriorly in the male, and in the anterior axillary line high in the axilla in the female just posterior to the lateral edge of the pectoralis major muscle. This is immediately attached to a water trap and the patient is asked to cough repeatedly or strain after deep inspiration with closed glottis, following which a portable semi-sitting or erect roentgenogram is made. If the lung is found to be completely expanded, the roentgenogram is repeated in 12 hours, and if the lung is still expanded at that time, the catheter is left in place but clamped. The roentgenogram is then repeated 12 hours

later, and if the lung is fully expanded, the catheter is removed. In the removal one should be careful not to permit any air to escape into the pleural cavity. A safe way to do this is to have the patient hold a deep breath and strain against the closed glottis during the removal. This technique is used whether the intercostal catheter decompression is used alone or in conjunction with instillation of glucose or insufflation of talc.

In the majority of cases treated by catheter and water trap decompression, the lungs were expanded without suction. In four after elapse of 24 hours without adequate expansion—constant suction of 10 to 14 cm. of water was used. This is a helpful adjunct to the therapy.

The use of a needle placed in the pleural cavity and fixed to the chest wall (Chandler,<sup>44</sup> Marriott and Foster-Carter<sup>45</sup>) appears to us to have the disadvantage of being easily dislodged and readily blocked. We feel that if one wishes to permit a *constant* egress of air from the pleural cavity, a catheter and not a needle should be used.

The advantage of earlier expansion by catheter decompression is shown by Hughes and Lowry<sup>46</sup> who averaged 11½ days for expansion in 27 out of 40 cases in which a catheter was used. As comparison they point out average expansion times without catheters as follows:

1 to 4 weeks - - - - -	Ornstein and Lercher <sup>26</sup>
4 weeks - - - - -	Rottenberg and Golden <sup>47</sup>
7 weeks - - - - -	Hyde and Hyde <sup>48</sup>
1 to 9 weeks - - - - -	Niehaus <sup>49</sup>
6 weeks to 2½ months -	Kjaergaard <sup>4</sup>

*Recurrent attacks and chronic pneumothorax.* Following our reasoning as the basis for treatment in our initial attacks, and considering the percentage of recurrences, it is logical then to either decompress immediately by catheter and/or follow up by thoracotomy in recurrent and chronic pneumothoraces. Those in distress due to the degree of loss of functioning pulmonary parenchyma are first decompressed and expanded by catheter, or at least decompressed by catheter, and then when the patient is without dyspnea, we follow this by thoracotomy. Patients not dyspneic are not decompressed if a thoracotomy is to be done. In those advanced in age or with associated marked pulmonary emphysema, or heart disease, or a combination of all three, treatment may end with expansion of the lung by catheter. This conservatism is open to some question, for a patient with lowered pulmonary function and/or cardiac reserve is more distressed and is certainly less capable of surviving repeated attacks of sudden reduction in pulmonary function than one who is otherwise well. We have taken this into account, and in 24 of the 34 recurrent cases of spontaneous pneumothorax operated, two had reduced cardiac reserve, one had considerable pulmonary emphysema and arteriosclerotic heart disease, and one was 73 years of age, besides being emphysematous with beginning cor pulmonale. Age in itself does not constitute a contra-indication for operation.

Thoracotomy in these cases consists of posterolateral incision, opening of the pleural cavity by rib resection or intercostal approach, removal of



blebs, bullae, or cysts by clamping relatively good lung proximal to the base of the lesion, and excision and suture closure (a second layer enfolds the first suture line). Airtight closure is checked by filling the pleural cavity with saline and having the anesthetist expand the lung with positive pressure. The saline is then removed and talc is placed on the costal surfaces of the lobes. Care is taken to keep the talc out of the mediastinum, off the mediastinal surface of the lobes, and off the diaphragmatic surface of the lower lobes. As the talc is placed, care is also taken to see that the chest wall muscle layers are not dusted by it. Intercostal drainage, antero- and posterolateral, is established and attached to water traps, and closure of the thoracotomy is done while the lung is inflated.

Operative interference in the past, as shown by reports, has a firm basis in the operative findings. Brock<sup>15</sup> (1948) operated eight of 46 cases, finding large cysts requiring excision or resection by lobectomy. Meade and Blades<sup>16</sup> (1949) reported eight recurrent and 11 chronic cases operated. In the eight recurrent cases, five had multiple blebs, and only in three were no findings noted. In the 11 chronic cases, three had ruptured bronchogenic cysts, five had leaking blebs, one had a bronchopleural fistula held open by an adhesion, and in only two were no causes found. Brewer, Dolley and Evans<sup>12</sup> (1950) found ruptured congenital cysts, blebs, or bullae in 14 out of 15 cases. Thus, in a total of 41 cases operated<sup>12,15,16</sup> there were obvious pathological findings in 35. In our series of 37 thoracotomies on 36 patients (one bilateral thoracotomy), findings of blebs, bullae, or cysts were noted in 33.

Cases which fail to respond promptly to methods of expansion have been shown by numerous authors to become chronic pneumothoraces in a considerable percentage. Haver and Clagett,<sup>17</sup> Babington,<sup>50</sup> Elghammer,<sup>51</sup> Hedgpeth et al,<sup>52</sup> Ehrlich,<sup>53</sup> and Kjaergaard<sup>4</sup> have all shown that if the pneumothorax is left unexpanded long enough, it will fail to expand. Thus, by temporizing and waiting in the case of chronic pneumothorax, one may have to decorticate the lung, as well as remedy the source of the leak, when surgery is finally done.

*Bilateral spontaneous pneumothorax.* The incidence as reported in the literature is, we feel, as with the unilateral spontaneous pneumothorax, no true index of its frequency. The understandable reluctance to report a single case, or at the most a few cases, certainly contributes to this. Oechsli<sup>54</sup> reviewed the literature up to 1934 and reported 77 bilateral spontaneous pneumothoraces. Glickmann and Schlomovitz<sup>55</sup> in 1936 increased this by review of the literature to 82 cases. Cooch<sup>30</sup> by 1948 collected 44 alternating spontaneous pneumothoraces to which he added one. Our addition of 13 cases (alternating and simultaneous pneumothoraces) is an indication that approximately 10 to 12 per cent of any large series of spontaneous pneumothoraces will be of the bilateral variety.

In instances of alternating collapse of the right and left lungs, unless there is a strong contra-indication to surgery, the patient should be given the protection of at least one lung that will remain expanded. This protection is even more important in cases of simultaneous collapse. There is no question in our minds that it is not elective, but imperative, that at

least one side be operated. Actually the same treatment should be afforded both types of cases, for it is purely fortuitous whether the patient is seen at any given time with an alternating or a simultaneous collapse. Three of our alternating pneumothorax cases gave a history of previous simultaneous collapse (one having had simultaneous collapse twice), and one of the two simultaneous cases gave a history of four attacks of previous alternating collapse.

*Spontaneous hemopneumothorax.* Kjaergaard<sup>4</sup> reported two out of 51 spontaneous hemopneumothoraces in the literature up to 1932. After a period of 10 years (1942), Hartzell<sup>56</sup> found 40 in the literature and added three of his own. In 1952 Holloway, Speir and Sadler<sup>14</sup> found 80 reported cases up to 1950 with 20 per cent mortality. All agree that the source of the bleeding is the tearing of a vascular adhesion with bleeding from either end of the adhesion. Holloway et al.<sup>14</sup> in their excellent article present cases demonstrating the need for thoracotomy. Their indication is soundly based, as is any indication for thoracotomy, in continued intrathoracic bleeding.

As stated, none of our six cases was operated because of continued bleeding. In reviewing the cases in detail, we feel that two of them were extremely fortunate to have survived with the only treatment being that of multiple thoracenteses. If the bleeding is from the pulmonary side of the torn adhesion, immediate expansion of the lung might be curative, depending on whether the bleeding is from the pulmonary or systemic circuit. Furthermore, it is most doubtful if pulmonary expansion will stop bleeding from the chest wall side unless it is part of a huge clot. Such a circumstance would hardly be desirable, for then the patient would surely require far more surgery (decortication).

In the future, we will follow the lead of Holloway et al.<sup>14</sup> in cases of continued bleeding and operate to ligate the source. With our knowledge today of blood replacement, it is not unreasonable to assume that the patient can be brought to surgery in relatively good condition and at a time most suitable for his survival.

### SUMMARY

We feel that all initial spontaneous pneumothoraces, unless practically expanded when first seen, should be promptly treated by intercostal catheter decompression. All cases of recurrent spontaneous pneumothorax, chronic pneumothorax, and bilateral recurrent pneumothorax should be treated by surgery as described. Spontaneous hemopneumothorax should be treated by prompt and energetic thoracentesis and operated when there is evidence of continuing intrapleural bleeding.

### RESUMEN

Creemos que todo neumotórax espontáneo inicial que no sea expandido cuando se ve por primera vez, debe tratarse inmediatamente por descompresión por la vía intercostal por medio del catéter. Todos los casos de neumotórax espontáneo recurrente y de neumotórax espontáneo bilateral

y neumotórax espontáneo crónico, deben tratarse por la cirugía como se ha descrito. El hemoneumotórax espontáneo, debe tratarse prontamente por toracentesis y se debe operar cuando hay evidencia de hemorragia intrapleurale continua.

### RESUME

Les auteurs estiment que les pneumothorax spontanés apparaissant pour la première fois devraient être rapidement traités par exsufflation à l'aide d'une ponction intercostale, sauf dans les cas où il sont pratiquement déjà en réexpansion quand ils sont vus. Tous les cas de pneumothorax récidivants bilatéraux devraient être traités chirurgicalement ainsi que les auteurs le décrivent. L'hémo-pneumothorax spontané doit être traité par une rapide et importante thoracenthèse et opéré quand il y a des signes d'hémorragie intrapleurale persistante.

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# Bronchogenic Carcinoma in East Pakistan

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## *Introduction*

At the turn of this century primary carcinoma of the lung was considered a rare disease but it has shown an amazing upsurge during the last 50 years. In some of the western countries more particularly the United States of America and the United Kingdom it now claims a higher toll of human life than gastric carcinoma which previously topped the list of death ascribed to cancer.

Three factors have been invoked to explain this alarming increase in the incidence of this disease. First, it is averred that the increase in the primary bronchogenic carcinoma may not be actual but may be due to its more frequent detection than formerly because of improvements in clinical diagnostic methods and pathological technique.

Second, it is ascribed to the change in the pattern of life brought about by the industrial revolution, especially the large scale mechanisation of transport and the universal use of automobiles, particularly in countries such as the United States of America.

Third, it is held that heavy smoking as reflected in the increase in production and sale of cigarettes during the last 50 years may be a causative factor. Investigations have sought to establish a direct relationship between the increase in bronchogenic carcinoma and cigarette smoking.

Thus, in the United States of America a great majority of the proved cases of bronchogenic carcinoma were found to have been amongst those addicted to heavy smoking for years. A corroborative observation is that, taken by and large, the bronchogenic carcinoma of the lung, especially the epidermoid type, is a disease of the male. In the event of a woman being the victim she has usually been observed to have been a heavy smoker.

The object of this paper is to record my experiences of this disease as observed in the Dacca Medical College Hospital which is about the only well-equipped hospital in East Pakistan with a population of 43 million people. The country is mostly under-developed and 90 per cent of its people live in villages leading an open air and agrarian life. Use of automobiles and the existence of tarred roads touch a microscopic fringe of the general population. The system of road communication is extremely undeveloped, the usual mode of transport being the country boats and bullock carts.

## *Materials:*

My observations on primary carcinoma of the lung began towards the end of 1950 when I took charge of 40 beds (30 males and 10 females) in the Dacca Medical College Hospital. The admission of patients followed

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the normal procedure, the only criterion of admission being the relative urgency of the condition of the patient. As a consequence, cases of remittent fever, pneumonias, appoplexy, nephritis and heart disease preponderated. Over a period of 18 months, total admissions to my ward were 1,586 of which 362 were cases of pulmonary disease, comprising chiefly the commoner affections such as lobar pneumonia, bronchial asthma, bronchiectasis, lung abscess, primary pleural effusions, etc. Amongst these, however, 20 cases were detected to be suffering from bronchogenic carcinoma. Unfortunately data of this disease in the hospital records during preceding years is not supported by requisite clinical and pathological investigations to be of statistical value.

### *Diagnosis:*

The following points were stressed in clinical examination and investigation:

I) Clinical History: Any patient aged 40 or above, with a history of haemoptysis for the first time was presumed to be a case of bronchial carcinoma unless it was proved otherwise.

II) Sudden appearance of respiratory complaints such as cough, breathlessness, localized pain in the chest in the above age-period were considered suspicious and were thoroughly investigated.

III) Neurological conditions as hemiplegia with Jacksonian convulsion in the paralyzed limb or with bilateral extensor planter reflex indicated special chest examination to exclude bronchogenic carcinoma.

### *Investigation:*

The following investigations were done as a routine:

(i) Blood counts and sedimentation rate; (ii) sputum examination for acid-fast bacilli, fungi and malignant cells; (iii) Fluoroscopy and radiography of the chest both postero-anterior and lateral. When indicated, the following examinations were also carried out:

(i) Bronchography; (ii) bronchoscopy; (iii) biopsy of the axillary or cervical lymph nodes whenever enlarged; and (iv) surgical exploration (one case only).

### *Facilities:*

In the absence of a chest unit no proper facilities yet exist for thoracotomy or pneumonectomy, but a few Pakistani doctors are receiving special training in this branch of surgery. Autopsy was performed on two cases only, as permission to carry out post-mortem is extremely difficult to secure for religious and sentimental reasons. Consequently, reliance had to be placed on clinical investigations and sputum examination for malignant cells.

### *Analysis of Cases:*

Detailed protocols of the cases in this series are given in Appendix. The salient features are tabulated below:

## TOTAL NUMBER OF CASES, 20.

*Sex:*

Male ..... 18

Female..... 2

TOTAL..... 20

*Age (in years):*

40-49 ..... 9

50-59 ..... 4

60-70 ..... 6

71-80 ..... 1

TOTAL..... 20

## OCCUPATION:

Male Cultivator (Paddy and Jute field laborers) ..... 11

Land Lord ..... 2

Business man ..... 2

Police Constable ..... 1

Clerk (Village school) ..... 1

Health Assistant ..... 1

Female Housewives ..... 2

TOTAL ..... 20

## ENVIRONMENT:

*Villagers (who never visited town before admission):*

Male ..... 11.

Female..... 1

*Born and brought up in town:*

Male ..... 1

Female..... 1

*Villagers (who visited town occasionally:*

Male ..... 6

TOTAL..... 20

## SMOKING HABITS:

*Heavy smokers:*

Male ..... 2

*Occasional smokers:*

Male ..... 4

*Non-smokers:*

Male ..... 12

Female..... 2

TOTAL..... 20

Method of smoking is somewhat different in this country in that the great majority of the people rarely smoke cigarettes. They use a locally made pipe known as "Hukka" in which the smoke passes through water before being inhaled. Crude tobacco is also smoked rolled up inside a "biri" leaf.

## SYMPTOMS AND SIGNS IN ORDER OF FREQUENCY:

Symptom	Number of Cases in Which Present	Duration
Cough .....	17	6 months to 2 years
Dyspnoea .....	15	6 months to 2 years
Pain in chest .....	10	3 to 6 months
Haemoptysis .....	10	4 to 10 months
Clubbing of fingers .....	8	Noticed during examination
Dysphagia .....	2	1 to 2 months
Enlarged nodes .....	2	1 to 3 months
Hoarseness of voice .....	1	2 weeks
Hemiplegia with,		
Jacksonian convulsion .....	1	1 month
with aphasia .....	1	3 months
Horner's syndrome .....	1	2 weeks
Fever, simulating pneumonia, pneumonitis with one or more of the above symptoms .....	8	3 to 6 months

## PREVIOUS ILLNESSES:

Malaria .....	9
Pneumonia .....	3
Pulmonary tuberculosis .....	1
Recurrent coryza in winter .....	3
Dysenteric symptoms .....	6
Heminthiasis:	
Round worm .....	5
Hook worm .....	3

*Case 1:* W.M., a muslim male, landholder, of 40 years, admitted on December 26, 1950 with cough, profuse expectoration, dyspnoea especially on lying down, progressive loss of weight and pain on the right side of his chest for nine months. Occasional fever, insomnia and anorexia supervened in the last two months. Past illness of recurrent attacks of malaria for eight years.

He was a non-smoker.

Clinical examination: Well built but emaciated, markedly anaemic and dyspnoeic. There was moderate clubbing of fingers. T=99°F, P/R=120/40 per min., B/p=106/72. Chest: Mediastinum Central. Sign of Consolidation on the right side. No abnormality in any other system. Blood: haemoglobin, 40 per cent; red cell, 2.5 million per cmm.; white cell count, 16,000 per cmm. with 80 per cent neutrophils; sedimentation rate, 65 mm./hr. Sputum, no acid-fast bacilli or fungi. Malignant cells present, epidermoid type. X-ray film revealed haziness on the right midzone with enlarged hilum shadow. There was a suspicion of erosion of fourth and fifth ribs. A penetrating film showed the erosion more clearly.

Remarks: General condition improved with antibiotics and supportive treatment but he left the hospital on January 31, 1951 on risk bond. At home he developed an abscess on the right side of inter-scapular region and he expired on February 2, 1952.

*Case 2:* M.H., a Muslim male, non-smoker, cultivator of 42 years was admitted on March 7, 1951 with the history of cough with blood-stained sputum, pain in the right side of the chest, irregular fever, progressive loss of weight for five months. Past history of malaria, dysentery and round worm for six years back.

Clinical examination: Build and nutrition fair, anaemic with early clubbing of fingers.

Chest examination: Revealed impaired resonance and diminished breath sounds with few moist sounds at the middle zone posteriorly. Other systems were found normal except a firm and three finger enlarged spleen.



Investigation: Blood picture was found normal except slight anaemia. Sedimentation rate, 70 mm./hr. Sputum examination showed malignant cells but no acid-fast bacilli or fungi. X-ray film revealed collapse of right middle lobe; bronchoscopy showed narrowing of the right middle lobe bronchus.

Progress: Haemoptysis and fever controlled, weight gained by four pounds after antibiotic and supportive treatment and was discharged.

*Case 3:* Z.A., a non-smoking Muslim male cultivator of 40 years was admitted on April 17, 1951 with a two month history of cough with expectoration, haemoptysis in moderate quantity and gradual loss of weight. Past history of cholera two years and malaria eight years back, pneumonia during childhood.

Clinical examination: Fair build and nutrition with clubbed fingers and anemia. T—99F, P/R—100/24 per min. Chest signs of collapse of the lower zone of the right lung. Other system normal.

Investigations: Blood picture was normal. Sedimentation rate, 50 mm./hr. Sputum examination revealed malignant cells but no acid-fast bacilli or fungi. X-ray film showed collapse of the right lower lobe. Bronchography revealed obstruction in the right lower lobe bronchus. Thoracotomy was done and he expired within a few hours. Autopsy showed bronchogenic carcinoma right lower lobe bronchus.

*Case 4:* Mrs. M.H., a Muslim married lady of 50 years was admitted on July 11, 1951 with a six month history of pain and swelling over the sternum, cough with scanty expectoration; and a recent history of swelling of left side of the neck with



CASE 3

tingling and burning sensation over the lateral half of her left hand, especially over the dorsum of left thumb, index and lateral half of middle finger. Past history of dysentery, 2 years back. Personal history, she was born and brought up in town, never smoked.

Clinical examination: Build and nutrition fair, moderately anaemic. Glands enlarged, hard and matted and very painful over the left supraclavicular and axillary region. T—99F. P/R—110/26 per min. Chest finding: a localized tender swelling about two inches in diameter was present over the manubrium. Diminished movement, impaired resonance and diminished breath over the left infra axillary region. Other system normal excepting diminished sensation over the distribution of the radial nerve.

Investigations: Blood picture moderate leucocytosis. Sedimentation rate, 55 mm./hr. Sputum, no acid-fast bacilli or malignant cells. X-ray film, an oval opacity in the left mid-zone bordering the chest wall. Biopsy of a cervical lymph node revealed adeno-carcinoma.

Remarks: Patient expired after 10 weeks at her residence.

**Case 6:** A.R., a Muslim male cultivator aged 50 years was admitted on October 14, 1951 with complaints of exertional dyspnoea and progressive loss of weight for one year, pain left side of the chest and dry cough for four months. He was a non-smoker. Had recurrent attacks of malaria for eight years and ankle loto-miasis for six years.

Clinical examination: He was fairly well built but very poorly nourished, markedly anaemic, and dyspnoeic. Odema present over the ankles and legs. Axillary and left supraclavicular lymph nodes palpable. P/R—104/38 per min. T—99F. B.P.—102/62 mm. of Hg. Chest findings, shifting of the mediastinum towards the right side. Cardiac apex was at fourth right intercostal space on the midclavicular line. Lung findings, signs of pleural effusion on the left side. No other abnormality.

Investigations: Haemoglobin 58 per cent, sedimentation rate 112 mm./hr. Sputum, no acid-fast bacilli or fungi seen. Malignant cells present. Pleural fluid was haemorrhagic. Biopsy of a right axillary lymph node showed metastatic malignancy. X-ray film revealed massive effusion on the left side.

Remarks: He signed the risk bond after three weeks stay in the hospital. His condition deteriorated.

**Case 10:** A.U. was a Muslim male aged 50 years, a village business man who was admitted on February 13, 1952 with a one month history of loss of power of right



CASE 10

extremities which started suddenly in the hand gradually involved his right arm, right thigh and leg.

Past history: Had attacks of dysentery and round worm infection for 20 years. Never smoked tobacco and visited town only twice after 1947.

Clinical examination: No anaemia, cyanosis or clubbing of fingers. Nervous system revealed upper motor neurone type of lesion of the right side. No sensory or visceral disturbance. Chest revealed no abnormality except a few crepitations in both bases. Other system normal. B/P—110/70.

On the night of admission at about 11 p.m. he suddenly started having spasms over his paralyzed arm which subsequently spread over the entire right side of the body. He did not lose consciousness and the attack continued for about 20 minutes. Next morning it was suspected to be a case of cortical lesion and he was screened in search of a primary focus. A rounded opacity was seen over the upper zone of the right lung.

His blood picture showed no significant change. Wasserman's Reaction, negative. Sputum, not available as he had no cough. X-ray film revealed a rounded circumscribed shadow in the right upper lobe.

He deteriorated rapidly with repeated convulsions and became unconscious before his death after a week. A partial post-mortem was done which revealed bronchogenic carcinoma in the posterior segmental bronchus of the right upper lobe. A growth occupying the upper half of the precentral gyrus was found on his left cerebrum.

### *Conclusions*

Although the period of study of this disease has been short, certain interesting features emerge from the analysis of the data presented. It will be observed that bronchogenic carcinoma is prevalent in East Pakistan to a significant degree even amongst those who are not in contact with tarred roads, who lead mostly an open air rural life and who are not addicted to cigarette smoking. A high proportion of cases gave a long antecedent history of cough and dyspnoea, but these symptoms are so common in persons of advanced age-groups that the patients disregarded them and rarely sought medical advice until collateral distressing symptoms supervened, such as, haemoptysis, pain in the chest, hoarseness of voice and dysphagia. In other cases the presenting syndrome were totally non-pulmonary in character such as hemiplegia, aphasia or a lump in the axilla or neck.

Cancer consciousness on the part of the physician was the most important factor in the diagnosis of these cases. Clinical examination in most of these cases revealed restriction of movement of one side of the chest or shifting of the mediastinum associated with clubbing of fingers, enlarged glands, etc.

This series confirms the preponderance of the disease amongst the males, the proportion of male to female patients being nine to one.

Occupational factors did not appear to influence the occurrence of the disease. Although bronchogenic carcinoma is known to give rise to widespread blood borne metastases, only cerebral and lymph node (cervical and axillary) metastases were detected in these cases.

## SUMMARY

1) Clinical data obtained from 20 cases of bronchogenic carcinoma observed during 18 months in Dacca Medical College Hospital, East Pakistan, have been analyzed.

2) Eighteen of these cases hailed from rural areas, where few tarred roads and automobiles are to be found. In most of the cases heavy smoking was not a factor.

3) Cough, dyspnoea, pain in the chest or haemoptysis in a person aged 40 years or above, should arouse suspicion of bronchogenic carcinoma and entail prompt and thorough investigation.

4) Cancer-consciousness on the part of the physician was found to be the determining factor in the diagnosis of these cases.

5) The series serves to bring out the fact that bronchogenic carcinoma is prevalent in East Pakistan to a significant degree. In the absence of reliable previous data its trend could not be determined. Further study of the disease is, therefore, of the utmost importance particularly with reference to etiologic or contributory factors other than tar or cigarette smoking.

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## RESUMEN

1) Se hace un análisis de los datos clínicos obtenidos en 20 casos de carcinoma bronquiogénico durante 18 meses en el Hospital de la Escuela de Medicina de Dacca en el Pakistan Oriental.

2) Dieciocho de estos casos, provenían de áreas rurales en las que se encuentran pocos caminos asfaltados y automóviles. En la mayoría, no existía el factor de tabaquismo acentuado.

3) La tos, la disnea, el dolor en el pecho o la hemoptisis en una persona de 40 o más años, debe despertar la sospecha del carcinoma bronquiogénico y ser seguida de una investigación pronta y completa.

4) El factor determinante para el diagnóstico, es el estado de alerta por parte del médico, frente a la posibilidad del cáncer.

5) Esta serie demuestra que el carcinoma bronquiogénico se encuentra en el Pakistan Oriental con una frecuencia significativa. Como faltan datos anteriores dignos de confianza, la tendencia no pudo determinarse. Un estudio ulterior de esta enfermedad, es por tanto, de extrema importancia en particular, respecto de los factores etiológicos o adyuvantes fuera del uso del cigarrillo o la presencia del asfalto.

## RESUME

1) L'auteur analyse les éléments cliniques de vingt cas de cancer bronchique observés pendant 18 mois à l'Hôpital du Collège Médical de Dacca (Pakistan de l'Est).

2) Dix-huit parmi ces cas provenaient de régions rurales, où il y a peu de routes goudronnées et d'automobiles. Dans la plupart de ces cas, les malades n'étaient pas de grands fumeurs.

3) La toux, la dyspnée, les douleurs thoraciques ou l'hémoptysie survenant chez un individu âgé de 40 ans ou davantage, devraient faire suspecter l'existence d'un cancer bronchique et déterminer des investigations rapides et complètes.

4) Il est apparu que ce qui avait avant tout permis le diagnostic, c'était le fait que le médecin eut connaissance de la possibilité du cancer.

5) Cette étude a démontré que le cancer bronchique existe d'une façon particulièrement fréquente dans le Pakistan de l'Est. La possibilité d'une extension actuelle ne peut pas être affirmée en l'absence d'éléments antérieurs valables. C'est pourquoi des études ultérieures sont de la plus haute importance, et elles doivent particulièrement porter sur l'étiologie ou sur les causes favorisantes d'autre nature que le goudron ou l'usage de cigarettes.

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# Bronchodilator Activity of Three New Drugs in Patients with Pulmonary Emphysema\*

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Many therapeutic agents have been employed effectively for the relief of bronchospasm. Preparations in current clinical use have been shown to be more efficacious than older ones, but no single agent has proved entirely satisfactory. Therefore, the present study was undertaken in order to evaluate the bronchodilator properties of three new drugs. As will be demonstrated, extensive preliminary observations showed that only one of these appeared to offer definite indications of therapeutic value. The bronchodilator activity of this drug was then studied in greater detail.

## PART I.

### *Method*

Seventeen male patients of average age 59, with intrinsic asthma or hypertrophic emphysema with clinical evidence of associated bronchospasm were studied.

Ventilometric measurements of vital capacity, maximum breathing capacity, volume of deep respiration, and breathing reserve were made with the Collins ventilometer. Although a number of additional tests were employed in this and other studies, these four appeared, in the experience of this laboratory, to provide a simple but reliable clinical measure of lung function. Observations on each subject were made on each of four separate days. The drugs studied, and their dosages, were as follows:

1) Paveril phosphate<sup>††</sup> a papaverine analogue - 50 mg.

2) Antrenyl<sup>††</sup> anticholinergic - 1.0 mg.

3) Drug 1313,<sup>††</sup> adrenergic - 10 mg.

Aminophylline, 0.5 Gm., was separately administered as a basis for comparison.

On each experimental day, the following routine was employed:

1) Slow (5 min.) intravenous injection of normal saline, 10 cc - control.

2) Ten minute interval.

3) Ventilometric measurements.

4) Ten minute rest period.

5) Slow (5 min.) intravenous injection of drug diluted to 10 cc. with normal saline. (The aminophylline was administered in 20 cc. volume as obtained from the ampoule.)

\*From the Veterans Administration Center, Los Angeles, California.

††Supplied through the courtesy of Eli Lilly and Company.

†Diethyl (2 - Hydroxyethyl) Methylammonium Bromide  $\alpha$  - phenyl - cyclohexane glycolate, supplied through the courtesy of Ciba Pharmaceutical Products, Inc.

††13,4-dihydroxy- $\alpha$ -isopropylamino propiophenone hydrobromide, supplied through the courtesy of Sharpe and Dohme, Inc.

TABLE I  
EFFECT OF INTRAVENOUS ADMINISTRATION OF DRUGS

Patient	Vital Capacity (Per cent Change)		Paveril Phosphate		1313		Aminophylline		Antrenyl		Volume of Deep Respiration (Per Cent Change)	
	Aminophylline	Antrenyl	Paveril Phosphate	1313	—	—	—	—	—	—	Paveril Phosphate	1313
1	-21	20	12	2	—	—	14	18	—	8	—	-10
2	2	6	1	-1	—	—	9	-5	—	-10	—	-11
3	0	17	-6	-2	—	—	-14	25	—	0	—	8
4	-24	-13	5	29	—	—	14	38	—	13	—	6
5	0	45	-7	-18	—	—	14	31	—	0	—	-6
6	-8	28	-11	-6	—	—	-6	11	—	0	—	12
7	-2	13	24	-4	—	—	20	45	—	0	—	-4
8	6	4	-6	-5	—	—	23	16	—	-27	—	-13
9	13	33	0	10	—	—	-10	13	—	-12	—	-22
10	9	2	-2	-6	—	—	0	35	—	18	—	13
11	-6	12	28	3	—	—	10	27	—	46	—	9
12	-4	21	-9	-9	—	—	20	25	—	9	—	15
13	14	17	-4	2	—	—	33	11	—	0	—	14
14	-4	0	7	6	—	—	14	6	—	-14	—	-4
15	-4	17	4	-9	—	—	0	23	—	0	—	71
16	20	40	20	22	—	—	40	33	—	15	—	7
17	22	13	5	7	—	—	-7	40	—	14	—	-8
Average	0.8	16.2*	3.6	1.2	—	—	10.2*	23.1*	—	2.6	—	4.5
S.D.	12.2	14.3	13.8	11.1	—	—	14.5	13.0	—	15.8	—	19.8

\* Statistically significant.



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Calcium Pantothenate	20 mg.
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Vitamin B <sub>12</sub> Activity	4 mcg.
Folic Acid	1.5 mg.
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